Effect of oral nutrition supplement on growth in preschool children – a systems physiology-based *in silico* analysis

V Hari Nishanthi[1*], Ekta Chheda[1*], Siranjeevi Gurumaani[2], Vani Gangwar[1], Abha Saxena[3], Karan Lomore[4], Madhavi Marathe[5], Preethi Rahul[6], Venkatesh Kareenhalli[7,8]

From [1]Associate Scientist, [2]Decision Scientist, [3]Scientist, [4]Product Manager, Metflux Research Private Limited, Mumbai, Maharashtra, India, [5]Senior Manager, [6]Manager, Nutricia International Private Limited (Danone), [7]Director, Metflux Research Private Limited, Mumbai, Maharashtra, India, [8]Professor, Department of Chemical Engineering, IIT Bombay, Mumbai, Maharashtra, India

**Equal contribution by both authors*

ABSTRACT

Introduction: Optimum nutrition is the cornerstone of child growth and development. Childhood is a period of rapid growth and development. Children of preschool age have higher nutritional needs and are often at risk of nutrient deficiencies. **Objective:** The present study was designed to evaluate the effect of an oral nutritional supplement (ONS) on growth parameters in a representative population. **Methods:** We used the systems-biology-based mathematical model for child growth to analyze the effect of ONS on growth in a representative *in silico* population of preschool children. The analysis included changes in average growth velocities of weight, height, muscle mass, fat mass, fat-free mass, and bone mass. We used meta-data analysis for evaluating the absorption of micronutrients present in the ONS that affects growth in preschool children. **Results:** The results of the analysis showed one serving of ONS in milk/day improved the weight gain velocity by 1.7 times in preschool children. The linear growth was 1.04 times higher than the control. The absorption of micronutrients such as iron, vitamin K, calcium, and magnesium was higher in the ONS group. **Conclusions:** This study indicates that the ONS containing macro and micronutrients, docosahexaenoic acid (DHA), and prebiotics can potentiate growth and development in preschool children. It provides micronutrients that can be readily absorbed which are essential for other vital functions in the body.

Key words: Macronutrients, Micronutrients, Physical growth, Prebiotics, Preschool children

It is a well-established fact that adequate nutrition in childhood enables optimum growth and development. The first 5 years of life is a period of rapid growth and development [1]. Nutrient intake and eating habits established in the early years of life have an impact on overall health in adulthood. Poor nutrition during these years alters growth and increases the risk of chronic diseases such as obesity, diabetes, and heart disease in later life [2].

As per the National Family Health Survey (NFHS-5), 36% of children <5 years of age were stunted, 19% were wasted, 32% were underweight, and 3% were overweight [3]. According to the Comprehensive National Nutrition Survey 2016–208, 18% of preschool children were anemic, 32% of preschool children had iron deficiency, and 14% of preschool children had vitamin D deficiency [4]. The NFHS-5 data indicates that about 67% of children in the age group of 6 months to 5 years had a certain degree of anemia. From this, about 29% of children had mild anemia, 36% had moderate anemia, and 2% of the children had severe anemia [3]. Deficiencies of essential vitamins and minerals can hamper physical growth and cognition [5].

One of the reasons for micronutrient deficiencies being common in preschool children is food neophobia (fear of trying new foods) and picky-eating behaviour. Researchers have observed that children with food neophobia have poor dietary diversity and consume less variety of foods [6]. As there is poor dietary diversity, milk finds a large place in children's diets. Although milk is believed to be a "complete" food, it lacks some essential micronutrients that are indispensable for growth and development. Cow's milk is a rich source of protein, fat, and calcium, but lacks iron, vitamin C, and vitamin D – which are essential for growth in children [7].

Apart from being nutritionally balanced, absorption of nutrients from food is crucial. From a nutrition standpoint, this is also important besides the amount present in a food. This is true for minerals like iron, wherein the absorption is influenced by enhancers like vitamin C, or inhibitors such as tannins and Calcium [8]. Therefore, ensuring the intake of micronutrients that

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Correspondence to: Venkatesh Kareenhalli, Department of Chemical Engineering, IIT Bombay, Mumbai, Maharashtra, India. E-mail: venks@metflux.in

are better absorbed in the given food matrix is important for the growth and overall well-being of children.

To bridge the unmet nutritional needs for achieving optimal growth in children, oral nutritional supplement (ONS) is commonly used. Several studies have shown that ONS positively influences growth and development and, hence, justifies their usage. The present study aims to evaluate the effect of an ONS on the growth outcomes such as height, weight, fat-free mass, muscle mass, and bone mass in preschool children. The rate of absorption of micronutrients such as iron, milk proteins, vitamin C, vitamin K, calcium, and phosphorus present in this ONS has also been studied.

MATERIALS AND METHODS

Model Description

We used the Kevin D. Hall mathematical model [9] and child model [10] to create a child growth model for predicting changes in metabolism, body weight, and energy homeostasis. The mathematical model consists of different pathways such as *de novo* lipogenesis, ketogenesis, lipolysis, gluconeogenesis, glycogenolysis, ketone excretion, glycerol gluconeogenesis, glucose-3-phosphate production rate, and gluconeogenesis, which are represented in the form of ordinary differential equations (ODEs). The model was benchmarked with the available data in the literature on the effect of macronutrients and micronutrients on physical growth (Table S1). The computational model was used to simulate diet perturbations that lead to adaptations of substrate selection and energy expenditure used to predict anthropometric and body composition changes in the population. Fig. 1 represents the simulation and analysis workflow that we adapted for this study. The macro and micronutrient content of the ONS was used as input parameters, while the output parameters included anthropometric data – weight, height, bone mass, and fat-free mass for this study.

Metabolic Pathway and Nutrients in the Model

The metabolic pathways that were perturbed to produce the desired outcomes were *de novo* lipogenesis, ketogenesis, lipolysis, gluconeogenesis, glycogenolysis, ketone excretion, glycerol gluconeogenesis, glucose-3-phosphate production rate, and gluconeogenesis. The available fat, glycogen, and protein pools translated into growth in terms of fat mass, fat-free mass, and weight (Fig. 2). The effect of some micronutrients such as zinc, calcium, iron, vitamin C, vitamin A, vitamin B12, and folic acid on the growth of the child was studied from the literature [11-16]. The cumulative effect [15] of such micronutrients was brought into the model by studying the fold change observed in the literature and by perturbing the metabolic pathways in the model these micronutrients effect was obtained in the *in silico* population.

Intervention Details

An *in silico* population of 2000 children that were representative of the overall population, of 3 to 5 years, with a mean weight 13.42 ± 1.91 kg and mean height 92.88 ± 6.17cm, was simulated using MatLab ODE solver (ODE 15s) [17] that solves a series of differential equations (which represent the physiological pathway) based on Runge-Kutta method. The simulated baseline characteristics of the population are described in Table 1. This population was simulated to receive 900–1200 kcal/day, 45–65% of calories as carbohydrates, 10–20% of calories as proteins, and 20–25% calories as fat and micronutrients such as folic acid, vitamin B12, zinc, iron, calcium, vitamin A, and vitamin C as a standard diet [18,19] (Table 2). This was referred to as the control group.

The same population of 2000 children was then simulated to receive an ONS 1 serve/day with milk in addition to the standard diet for 6 months. This group was referred to as the ONS group. The details of the nutrient composition of the ONS (AptaGrow, Nutricia International Pvt. Ltd., Danone India) product that was used in the model simulation analysis are mentioned in the supplementary materials (Table S2).

Meta-Data Analysis

Meta-data analysis refers to the statistical analysis of the data from independent primary studies that address the same research question, and aims to generate a quantitative estimate of the studied phenomenon [22]. We used Monte-Carlo simulations [23] to conduct a meta-data analysis to compare the micronutrient absorption rate among the control and ONS group. Monte Carlo simulation is used to generate a set of random numbers according to the data distribution (normal and others) and parameters for each variable data (Please refer to the supplementary materials for the details). From the data available in the literature, statistical parameters (mean and standard deviation) were obtained, and

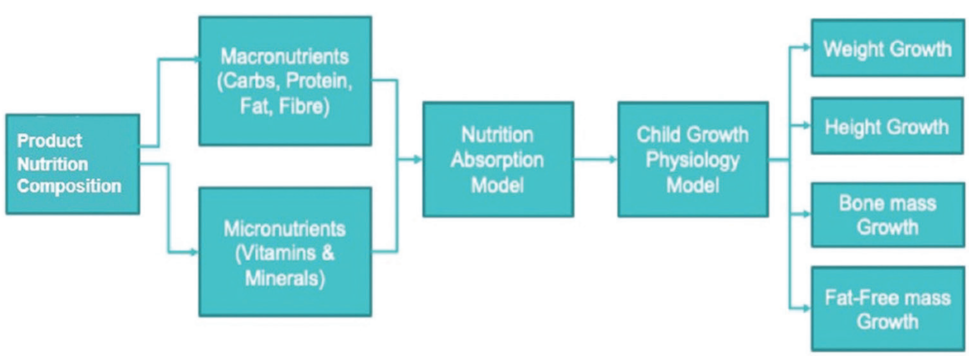

Figure 1: Simulation and analysis workflow diagram

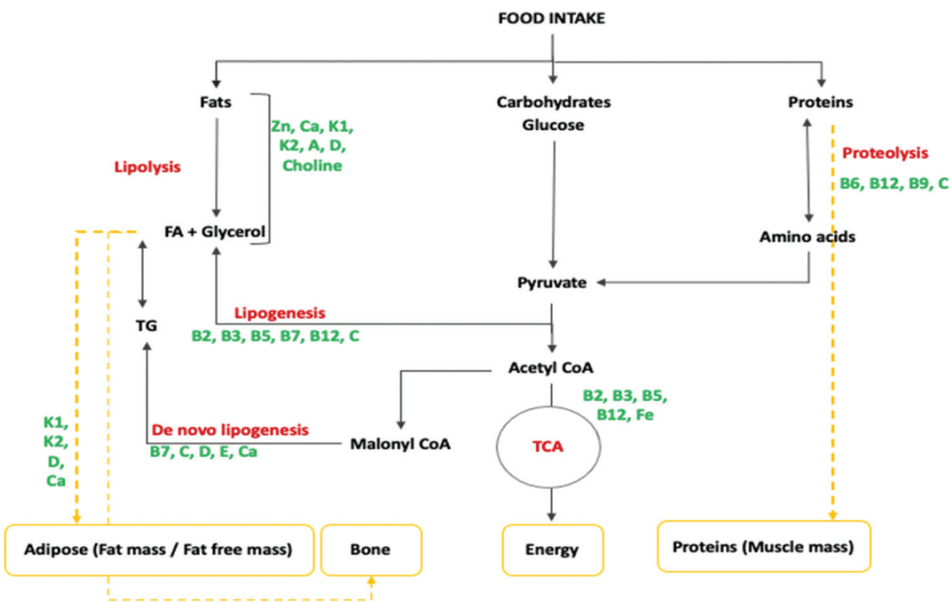

Figure 2: Schematic representation of model network showing the molecular targets of micronutrients on metabolic pathways that affect growth

Table 1: Baseline characteristics of the control group and ONS group

Characteristics	Control group	ONS group
Population size (n)	2000	2000
Ratio of girls: Boys	1:1	1:1
Weight (kg)*	13.42±1.91	13.42±1.91
Height (cm)*	92.88±6.17	92.88±6.17

Data represented as mean±standard deviation. Kilo calorie is calculated from the energy density per gram of carbohydrate (4.0 Kcal/g), protein (4.0 Kcal/g) and fat (9.0 Kcal/g) [20]. *Weight and height were taken as per the IAP standards for 3 to 5 years old children [21]

Table 2: Calorie and macronutrient composition of the control group and ONS group used for model simulation

Nutrients	Control group	ONS group
Calories (kcal)	997±58.3	1213.3±58.3
Carbohydrates (%)	57.5	57.5
Protein (%)	14.4	14.8
Fat (%)	21.9	22.7

Calories are represented as mean±standard deviation, ONS: Oral nutrition supplement

an *in silico* population was simulated to represent pre- and post-values for the level of micronutrient absorption.

RESULTS

The results of the model simulation are described below. The results are discussed in two sections – 1. Physical growth parameters and 2. Micronutrient absorption.

Physical Growth Parameters

Physical growth is used as an indicator to reflect nutritional status in children. Some of the parameters that are used to indicate physical growth are weight, height, muscle mass, bone mass, and fat-free mass. The results of this analysis compared the effect of supplementation on different growth parameters of the control and ONS groups after 6 months.

The mean weight gain velocity in the control group was 0.26 ± 0.09 kg/month versus 0.44 ± 0.1 kg/month in the ONS group. About 80% of the population experienced an improved weight gain in the ONS group (16.03 ± 1.57 kg) as compared to the control group (14.96 ± 1.62 kg) at the end of 6 months of analysis (Fig. 3a and b). The difference in the weight gain velocity was statistically significant when the population was simulated with ONS ($p<0.0005$).

The analysis showed that the mean height and height gain velocities of the ONS group were 105.62 ± 2.16 cm and 2.12 ± 0.74 cm/month, respectively. The mean height and height gain velocities of the control group were 105.03 ± 2.19 cm and 2.02 ± 0.73 cm/month, respectively; indicating a higher rate of height gain in the ONS group (Fig. 3c and d).

About 98.2% of the population in the ONS group had a higher mean fat-free mass (FFM) (13.48 ± 1.21 kg) as compared to the control group (12.45 ± 1.26 kg). The mean FFM gain rate was also higher in the ONS group (0.42 ± 0.09 kg/month) as compared to the mean FFM gain rate of the control group (0.25 ± 0.09 kg/month). The fold change in FFM in the ONS group was 1.68 times faster than in the control group. The difference in the FFM gain velocity was statistically significant ($p\leq0.0005$) in the ONS group (Fig. 4a and b).

The simulation results showed that children in the ONS group had a muscle mass of 12.97 ± 1.14 kg, while that of the children in the control group was 12.01 ± 1.19 kg. About 97.8% of the population in the ONS group had a higher gain rate of the mean muscle mass (0.4 ±0.09 kg/month) than that of the control group (0.24 ± 0.09 kg/month). In terms of fold change, children in the ONS group had a 1.66 times higher rate of muscle mass gain as compared to the children in the control group (Fig. 4c and d).

It was observed that 70% of the population in the ONS group had a higher mean bone mass (0.64 ± 0.06 kg) and bone mass

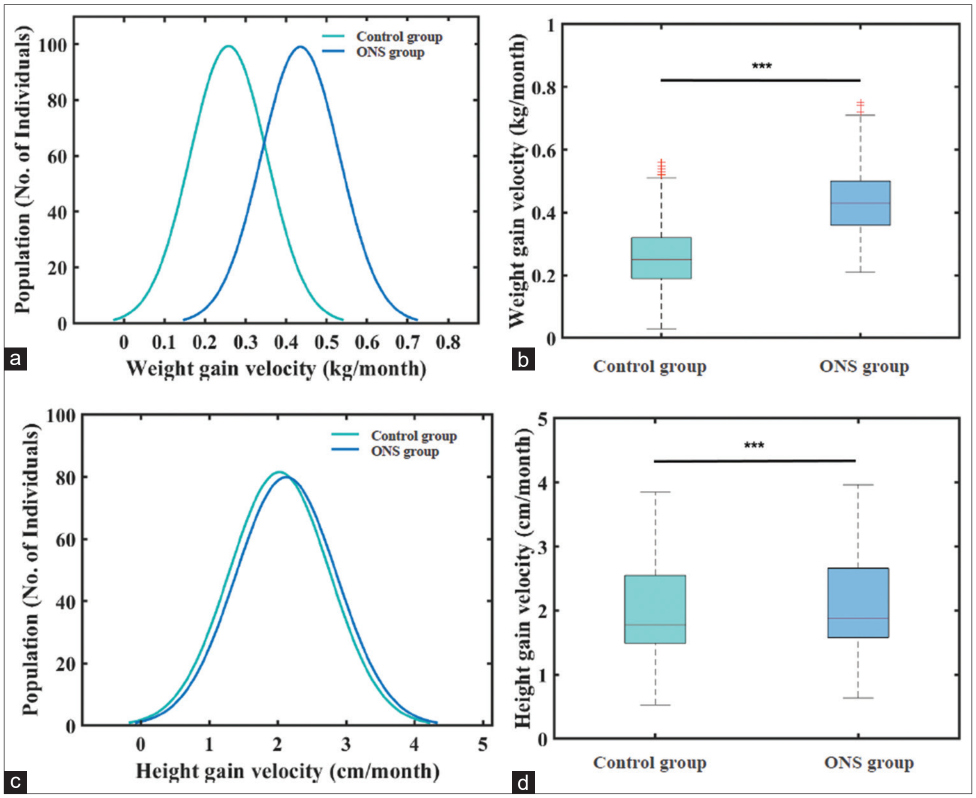

Figure 3: Comparison of weight and height gain velocities among control (standard diet) and ONS group (standard diet + ONS 1 serve/day) at the end of 6 months. (a) Population distribution for weight gain velocity of the control group and ONS group. (b) Box plot representation for weight gain velocity among the two groups (*p≤0.0005). (c) Population distribution for height gain velocity of control and ONS group. (d) Box plot representation for height gain velocity among the two groups (*** p≤0.0005)**

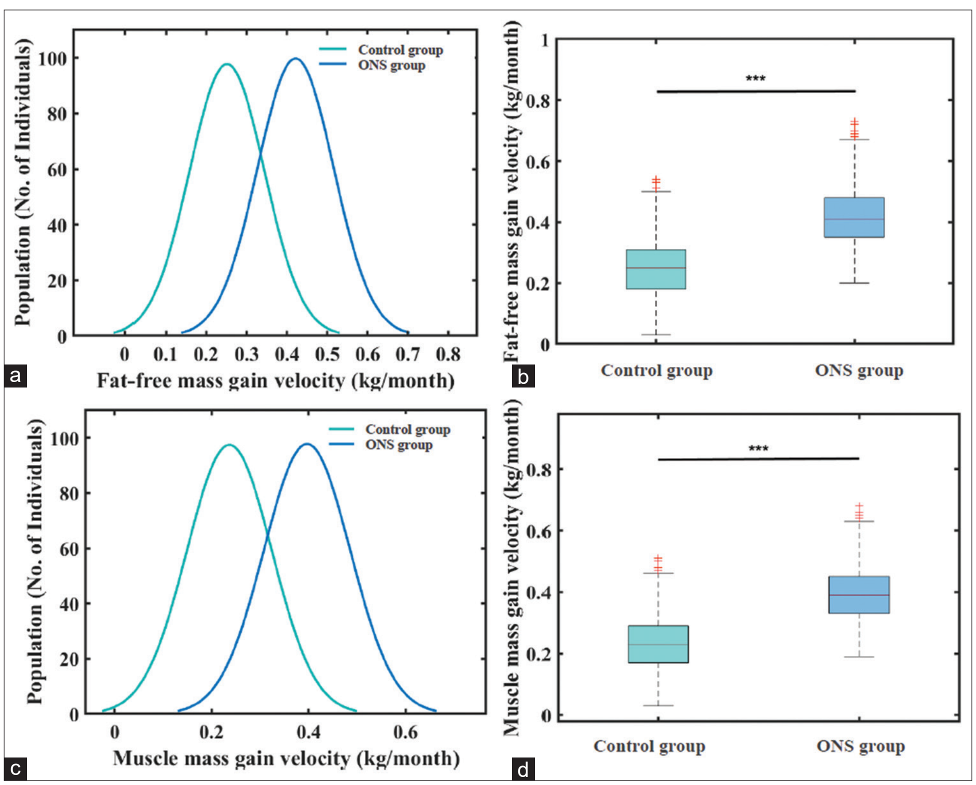

Figure 4: Comparison of fat-free mass and muscle mass gain velocities among control (standard diet) and ONS group (standard diet + ONS 1 serve/day) at the end of 6 months. (a) Population distribution for fat-free mass gain velocity of the control group and ONS group and (b) Box plot representation for fat-free mass gain velocity among the two groups (*p≤0.0005). (c) Population distribution for muscle mass gains velocity among control and ONS group. (d) Box plot representation for muscle mass gain velocity among the two groups (***p≤0.0005)**

gain rate (0.017 ± 0.005 kg/month) as compared to the mean bone mass (0.6 ± 0.06 kg) and bone mass gain rate (0.01 ±0 kg/month) of the control group (Fig. 5). The fold change in the rate of bone mass gain of children consuming ONS was 1.7 times higher than that of the children in the control group.

Micronutrient Absorption Analysis

The absorption of micronutrients is an important factor in determining growth and gut health in children. In this section, we describe the results of the analysis based on meta-data analysis. The effect of galacto-oligosaccharides (GOS) on iron absorption and gut microbiota, ascorbic acid: Iron molar ratio, vitamin K2 bioavailability, the effect of Fructo-oligosaccharides (FOS) on magnesium absorption, the effect of vitamin D on calcium absorption, and the effect of calcium on phosphorus absorption was analysed using meta-data analysis [24-29].

The effect of GOS on iron absorption [24] between the control and ONS groups was analyzed using meta-data analysis. The fold change in the percentage of iron absorption in children belonging to the ONS group was 1.6 times more than children in the control group (Fig. 6). About 89% of the population in the ONS group had higher iron absorption as compared to the control population (Fig. 6a). The difference in iron absorption was statistically significant in the ONS group ($p<0.0005$) [24].

We studied the effect of the ascorbic acid to iron molar ratio on the percentage of fractional iron absorption among the two groups. In the presence of ascorbic acid: iron molar ratio of 2:1, there was a significantly higher fold change (3.76 times) in the percentage of fractional iron absorption versus the absence of ascorbic acid (Fig. 6b). Nearly, 98% of the population who belonged to the ONS had better iron absorption than the control population. There was a significant positive effect on the plasma ferritin levels in the population in the ONS group containing GOS versus the population without GOS ($p<0.05$) (Fig. 6c) [25].

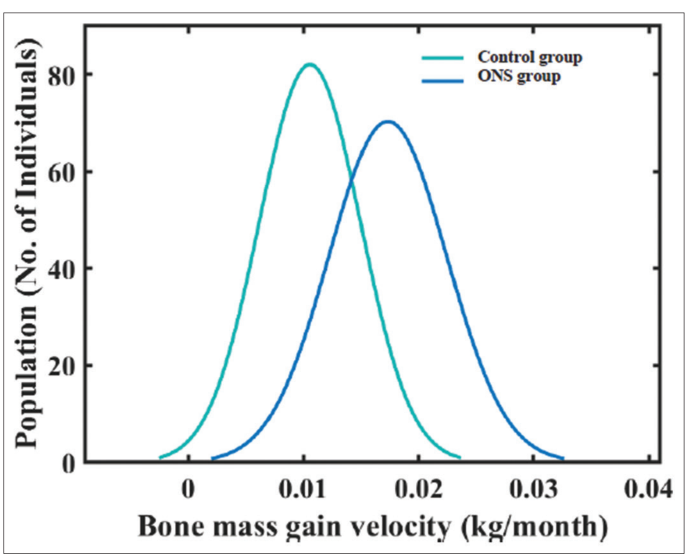

Figure 5: Population distribution for bone mass gain velocities among the control group (standard diet) and ONS group (standard diet + ONS 1 serve/day) at the end of 6 months

We analyzed the effect of the simulation of iron absorption on the *Bifidobacterium* copies between the two groups. It was seen that iron absorption increased the beneficial microbes in the gut in the population that was simulated to receive GOS through the ONS medium, versus the population without GOS (control group). The fold change in *Bifidobacterium* copies in the ONS group was 1.99 times higher than in the control group. The simulation results showed that 97% of children from the ONS group had higher *Bifidobacterium* copies and the difference was statistically significant in the population that was simulated to receive ONS as compared to the control group ($p<0.05$) (Fig. 7a) [24].

We studied the effect of FOS on magnesium absorption between the two groups. The fold change was 1.2 times higher in the ONS group as compared to the control group. Around 63% of the population in the ONS group had improved magnesium absorption than the control population (Fig. 7b). The difference in the rate of magnesium absorption was statistically significant for the ONS group compared to the control ($p<0.05$) [27].

We compared the population distribution for vitamin K bioavailability using meta-data analysis between control and ONS groups (Fig. 7c). There was a dramatic increase (8.2 times) in serum vitamin K in the ONS group as compared to the control group. A 100% of the population that belonged to the ONS group had higher mean vitamin K levels. The difference in the vitamin K levels was statistically significant in the ONS group viz-a-viz the control group ($p<0.0005$) [26].

Next, we studied the effect of calcium on phosphorus absorption between the two groups. The fold change in phosphorus absorption was 1.2 times higher in the ONS group (fortified with calcium) versus in the control group (without calcium) (Fig. 8a). About 80% of the population in the ONS group had improved serum phosphorus levels and the difference in the absorption rate in the ONS group was also statistically significant ($p<0.05$) [29].

We compared the effect of vitamin D on bone mineral content (BMC) and calcium absorption (Fig. 8b and c). In the population that was simulated to receive ONS (with Vitamin D), the fold change in BMC was 1.3 times higher as compared to the control population (without Vitamin D). About 60% of the population in the ONS group had better BMC as compared to the control population. The difference in the BMC was statistically significant in children that were simulated to receive ONS versus those that were simulated to receive a standard diet alone ($p<0.05$) [28].

The children that were simulated to receive the ONS had a fold change of 1.1 in serum calcium as compared to the children that were simulated to receive a standard diet alone (control group). Nearly, 82% of the children in the ONS had higher serum calcium levels as compared to the children in the control group. The difference in calcium levels was statistically significant in the ONS group ($p<0.05$) versus that of the control group [28].

DISCUSSION

Growth in children is affected/influenced by different factors. One of the most important factors in determining growth and

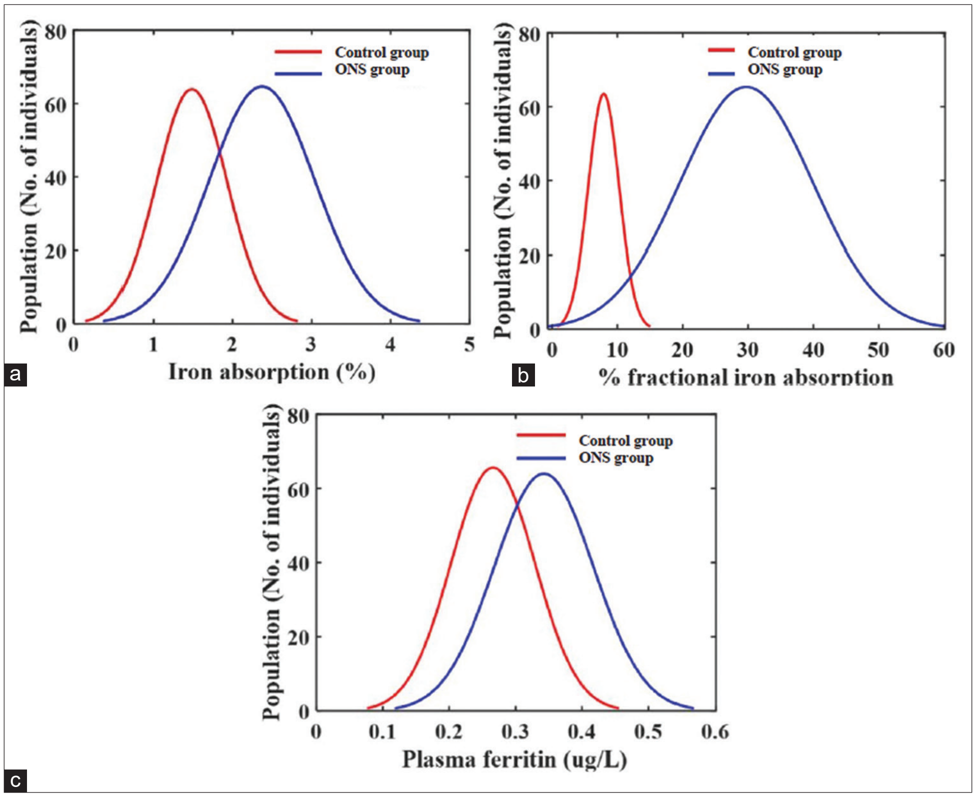

Figure 6: Comparison of iron absorption and plasma ferritin levels among the control group (standard diet) and ONS group (standard diet + ONS 1 serve/day) at the end of 6 months. (a) Population distribution for iron absorption percentage among control and ONS group. (b) Population distribution for percentage fractional iron absorption among the control group (absence of ascorbic acid: Iron molar ratio) and ONS group (ascorbic acid: Iron molar ratio of 2:1). (c) Population distribution for plasma ferritin levels among control and ONS group

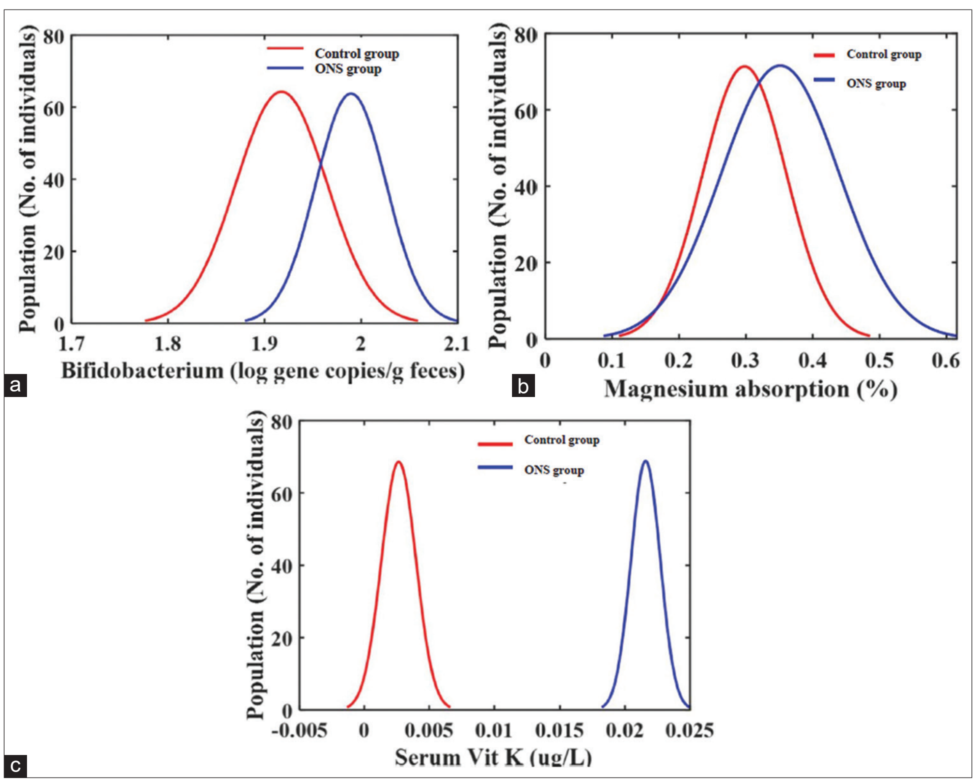

Figure 7: Comparison of Bifidobacterium copies, magnesium absorption, and vitamin K levels among the control group (standard diet) and ONS group (standard diet + ONS 1 serve/day) at the end of 6 months. (a) Population distribution of *Bifidobacterium* copies among the control group and ONS group. (b) Population distribution of magnesium absorption percentage among the control group and ONS group. (c) Population distribution of serum vitamin K among the control group and ONS group

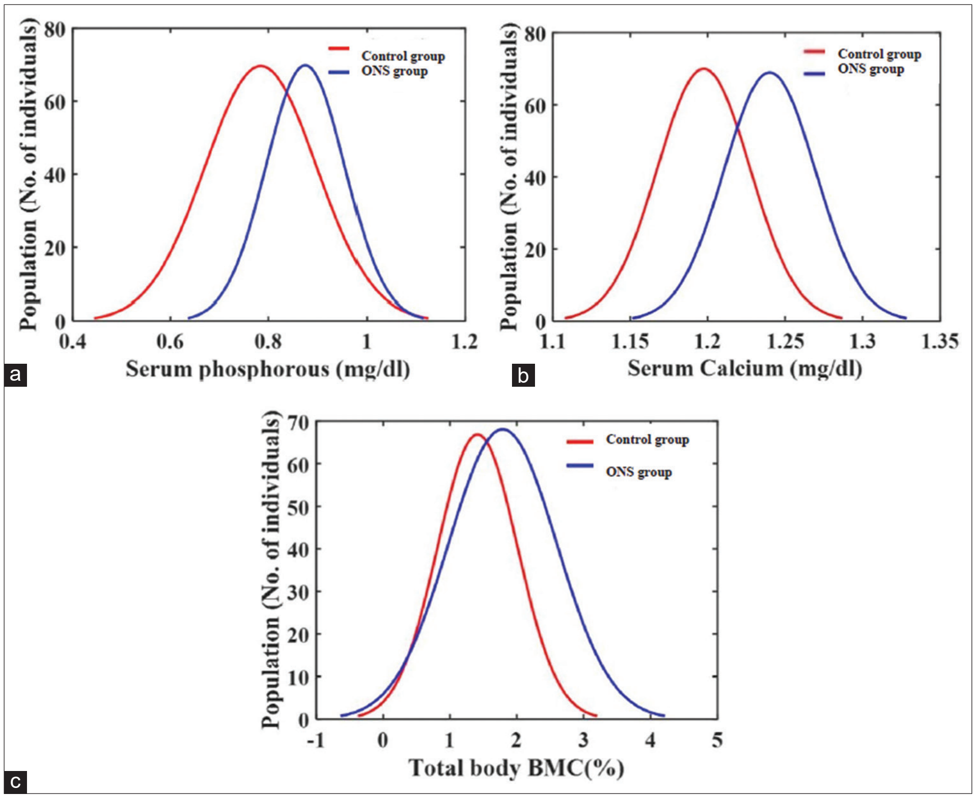

Figure 8: Comparison of serum phosphorus, serum calcium and percentage total body bone mineral content (BMC) among the control group (standard diet) and ONS group (standard diet + ONS 1 serve/day). (a) Population distribution of serum phosphorus among control and ONS group. (b) Population distribution of serum calcium among control and ONS groups. (c) Population distribution of % total BMC among control and ONS groups

development in children is adequate and wholesome nutrition during the early years [30]. The present study analyzed the effect of an ONS on physical growth and micronutrient absorption in preschool children.

Simulation results showed significant positive effect on the velocities of physical growth parameters such as weight, height, fat-free mass, muscle mass and bone mass in the population that received 1 serve/day of ONS versus in that of population that received a standard diet alone. Savarino *et al*., in 2021 [31], describe how macronutrients and energy are required for enhancing growth and development throughout childhood. The results from our analysis can similarly be attributed to the macronutrients and calories in the ONS that was provided to the children in addition to their regular diet.

In this context of macronutrients, one serving ONS contains 4.5 g of added sugar (sucrose). This added sugar. The World Health Organization recommends consuming <10% of total calories as sugar [32]. Taking this into consideration, one serving ONS with milk (given as an intervention in our study) contains about 1.5–2% of total calories as sugar. Assuming that some amount of sugar would also be coming from the standard diet, it is well within the recommended amount of sugar intake/day for children.

Hoffman and Falvo, in 2005, have studied the absorption and mechanism of milk proteins. β-Casein is the major component of protein present in milk. Milk protein is beneficial due to its ability to nutrient uptake and the presence of biologically active peptides. Casein is a complete protein and exists in the form of a micelle. This forms a gel in the gastrointestinal system when consumed, causing an efficient nutrient supply and a sustained release of amino acids. This causes better nitrogen utilization by the body [33]. The ONS in the present study contains 100% milk protein and thus has a beneficial effect on overall growth and increase in bone mass.

Singh, in 2009, in his study, stated that micronutrients play an essential role in improving immunity, cognition, and brain development in children [34]. While several of the available pediatric ONS contain a variety of micronutrients, the absorption efficiency of these micronutrients is crucial for them to carry out vital functions [35].

The ONS, in this study, contains micronutrients that are readily absorbed by the body. The ONS is enriched with prebiotics such as galacto-oligosaccharides and fructo-oligosaccharides, which, selectively, enhance the growth of colonic bacteria that are beneficial for the body. They increase the colonic production of short-chain fatty acids that decrease the luminal pH. Due to this function, prebiotics enhances the absorption of minerals such as iron, calcium, and magnesium [24]. This finding has been consistent with our analysis of the effect of the simulation of GOS on iron absorption. GOS has also shown promising results in increasing beneficial microbes like *Bifidobacterium* in our study. This helps in improving gut health and supporting immunity.

The results of our analysis showed that supplementing a nutritional drink with the optimum amount of micronutrients helped in improving iron stores (plasma ferritin) and hemoglobin levels. Pauline *et al*., in 2018, have described how calcium is known to be a competitive inhibitor of iron absorption in children. The addition of ascorbic acid markedly improves iron absorption from cow's milk or any fortified milk [36]. This inhibitory effect of calcium on iron absorption has been attenuated by the addition of ascorbic acid in the 2:1 ascorbic acid to iron molar ratio. Walczyk *et al*., in 2014, reported a similar finding in their study [25].

Vitamin K2 is known to be more effective than vitamin K1 in physiological functions such as improving bone health [37]. ONS contains vitamin K in the form of K2. It was seen from our analysis that all the children who were given vitamin K2 containing ONS had improved vitamin K absorption. A similar finding has been reported by Schurger 2007 in his study [26] on vitamin K and its forms.

The ONS is enriched with FOS – a prebiotic. A study [27] conducted by Van Den Heuvel *et al*., in 2009, showed that FOS enhanced the absorption of magnesium. Our analysis indicated a similar finding. Magnesium improves bone health and this was consistent with the study done by Abrams *et al*., 2021 on evaluating the effect of magnesium absorption on bone mineral density and bone mineral content in 4-year-old children [38].

Vitamin D enhances calcium absorption [28]. Calcium is essential for improving bone mineral content and bone health [39]. Our analysis showed that 60% of the children in the ONS had higher bone mineral content versus children in the control group, which was a consistent finding by Du *et al*., 2004 [40]. Furthermore, a significantly higher proportion of the population of children who belonged to the ONS had improved calcium absorption.

Phosphorus absorption increases in presence of calcium [29]. Calcium interacts with phosphorus in many ways. High calcium intake can inhibit phosphorus uptake from the gut, and a high phosphorus intake may decrease the absorption of calcium, both due to the formation of calcium-phosphate salts [39]. Hence, maintaining an optimal ratio of these minerals is important. The ONS contains the right amount of calcium, which was shown to improve phosphorus levels.

Limitations of the Study

Our study had certain limitations. This was an *in silico*-based study analysis of the effect of oral nutrition supplements on growth in preschool children. A clinical study in this capacity needs to be carried out to validate the results of our *in silico* analysis.

CONCLUSIONS

The present study aimed to evaluate the effect of an ONS on physical growth in preschool children. Our simulation analysis indicated that 6 months of supplementation with the given ONS consisting of the aforementioned macro and micronutrients significantly improved the growth parameters in preschool-aged children. The present systems-biology-based study suggests that one serving per day of the Oral Nutrition Supplement (AptaGrow, Nutricia International Pvt. Ltd., Danone India) enhanced growth parameters in preschool children. The meta-data analysis showed the ONS contained micronutrients that had improved absorption rates. ONS would help bridge the nutrition gaps in preschool children when the requirements are not met adequately [41].

REFERENCES

1. Bliznashka L, Perumal N, Yousafzai A, Sudfeld C. Diet and development among children aged 36-59 months in low-income countries. Arch Dis Child 2022;107:719-25.
2. Jarman M, Edwards K, Blissett J. Influences on the dietary intakes of preschool children: A systematic scoping review. Int J Behav Nutr Phys Act 2022;19:20.
3. International Institute of Population Sciences Deonar Mumbai. National Family Health Survey (NFHS-5), 2019-21 India Report. Mumbai: International Institute of Population Sciences Deonar; 2022.
4. Ministry of Health and Family Welfare (MoHFW) Government of India UNICEF and Population Council 2019 Comprehensive National Nutrition Survey (CNNS) National Report New Delhi. Comprehensive National Nutrition Survey: 2016-2018. New Delhi: Ministry of Health and Family Welfare; 2016.
5. Rivera JA, Hotz C, González-Cossío T, Neufeld L, García-Guerra A. The effect of micronutrient deficiencies on child growth: A review of results from community-based supplementation trials. J Nutr 2003;133:4010S-20S
6. Wolstenholme H, Kelly C, Hennessy M, Heary C. Childhood fussy/picky eating behaviours: A systematic review and synthesis of qualitative studies. Int J Behav Nutr Phys Act 2020;17:2.
7. Graczykowska K, Kaczmarek J, Wilczynska D, Łos-Rycharska E, Krogulska A. The consequence of excessive consumption of Cow's milk: Protein-losing enteropathy with anasarca in the course of iron deficiency anemia-case reports and a literature review. Nutrients 2021;13:828.
8. Pizarro F, Olivares M, Maciero E, Krasnoff G, Cócaro N, Gaitan D. Iron absorption from two milk formulas fortified with iron sulfate stabilized with maltodextrin and citric acid. Nutrients 2015;7:8952-9.
9. Hall KD. Predicting metabolic adaptation, body weight change, and energy intake in humans. Am J Physiol Endocrinol Metab 2010;298:E449-66.
10. Hall KD, Butte NF, Swinburn BA, Chow CC. Dynamics of childhood growth and obesity: Development and validation of a quantitative mathematical model. Lancet Diabetes Endocrinol 2013;1:97-105.
11. Hadi H, Stoltzfus RJ, Dibley MJ, Moulton LH, West KP Jr., Kjolhede CL, *et al*. Vitamin A supplementation selectively improves the linear growth of Indonesian preschool children: Results from a randomized controlled trial. Am J Clin Nutr 2000;71:507-13.
12. Angeles IT, Schultink WJ, Matulessi P, Gross R, Sastroamidjojo S. Decreased rate of stunting among anemic Indonesian preschool through iron supplementation. Am J Clin Nutr 1993;58:339-42.
13. Kvestad I, Taneja S, Kumar T, Hysing M, Refsum H, Yajnik CS, *et al*. Vitamin B12 and folic acid improve gross motor and problem-solving skills in young North Indian children: A randomized placebo-controlled trial. PLoS One 2015;10:e0129915.
14. Mozaffari-Khosravi H, Shakiba M, Eftekhari MH, Fatehi F. Effects of zinc supplementation on physical growth in 2-5-year-old children. Biol Trace Elem Res 2009;128:118-27.
15. Shim JO, Kim S, Choe BH, Seo JH, Yang HR. Effect of nutritional supplement formula on catch-up growth in young children with nonorganic faltering growth: A prospective multicenter study. Nutr Res Pract 2020;14:230-41.
16. Specker B, Binkley T. Randomized trial of physical activity and calcium supplementation on bone mineral content in 3-to 5-year-old children. J Bone Miner Res 2003;18:885-92.
17. Shampine LF, Reichelt MW. The matlab ode suite. SIAM journal on scientific computing 1997;18:1-22.
18. National Institute of Nutrition. Dietary Guidelines For Indians-a Manual. Hyderabad: National Institute of Nutrition; 2011.
19. U.S. Department of Health and Human Services, Office of Disease Prevention and Health Promotion. Appendix E-3.1. Nutritional Goals for Each Age/Sex Group Used in Assessing Adequacy of USDA Food Patterns

at Various Calorie Levels 2015. Available from: https://www.health.gov/our-work/nutrition-physical-activity/dietary-guidelines/previous-dietary-guidelines/2015/advisory-report/appendix-e-3/appendix-e-31a4 [Last accessed on 2022 Sep 19].
20. Chapter 3: Calculation of the Energy Content of Foods-Energy Conversion Factors; n.d. Available from: https://www.fao.org/3/y5022e/y5022e04.htm [Last accessed on 2022 Sep 19].
21. Indian Academy of Pediatrics (IAP). IAP Growth Charts. Navi Mumbai: Indian Academy of Pediatrics; n.d. Available from: https://www.iapindia.org/iap-growth-charts [Last accessed on 2022 Sep 19].
22. Komarova SV, Mikolajewicz N. Meta-analytic methodology for basic research: A practical guide. Front Physiol 2019;10:203.
23. Saxena A, Ravutla S, Upadhyay V, Jana S, Murhammer D, Giri L. Statistical modeling of cell-to-cell variability in viral infection during passaging in suspension cell culture: Application in Monte-Carlo simulation. Biotechnol Bioeng 2020;117:1483-501.
24. Paganini D, Uyoga MA, Cercamondi CI, Moretti D, Mwasi E, Schwab C, *et al*. Consumption of galacto-oligosaccharides increases iron absorption from a micronutrient powder containing ferrous fumarate and sodium iron EDTA: A stable-isotope study in Kenyan infants. Am J Clin Nutr 2017;106:1020-31.
25. Walczyk T, Muthayya S, Wegmüller R, Thankachan P, Sierksma A, Frenken LG, *et al*. Inhibition of iron absorption by calcium is modest in an iron-fortified, casein-and whey-based drink in Indian children and is easily compensated for by addition of ascorbic acid. J Nutr 2014;144:1703-9.
26. Schurgers LJ, Teunissen KJ, Hamulyák K, Knapen MH, Vik H, Vermeer C. Vitamin K-containing dietary supplements: Comparison of synthetic Vitamin K1 and natto-derived menaquinone-7. Blood 2007;109:3279-83.
27. van den Heuvel EG, Muijs T, Brouns F, Hendriks HF. Short-chain fructo-oligosaccharides improve magnesium absorption in adolescent girls with a low calcium intake. Nutr Res 2009;29:229-37.
28. Heaney RP, Dowell MS, Hale CA, Bendich A. Calcium absorption varies within the reference range for serum 25-hydroxyvitamin D. J Am Coll Nutr 2003;22:142-6.
29. Kutluk G, Çetinkaya F, Başak M. Comparisons of oral calcium, high dose Vitamin D and a combination of these in the treatment of nutritional rickets in children. J Trop Pediatr 2002;48:351-3.
30. UNICEF. Nutrition UNICEF. New York, United States: United Nations International Children's Emergency Fund; n.d. Available from: https://www.unicef.org/nutrition [Last accessed on 2022 Aug 05].
31. Savarino G, Corsello A, Corsello G. Macronutrient balance and micronutrient amounts through growth and development. Ital J Pediatr 2021;47:109.
32. World Health Organization. WHO Calls on Countries to Reduce Sugars Intake Among Adults and Children. Geneva: World Health Organization; n.d. Available from: https://www.who.int/news/item/04-03-2015-who-calls-on-countries-to-reduce-sugars-intake-among-adults-and-children [Last accessed on 2022 Nov 24].
33. Hoffman JR, Falvo MJ. Protein-which is best? J Sports Sci Med 2004;3:118-30.
34. Singh M. Role of micronutrients for physical growth and mental development. Indian J Pediatr 2004;71:59-62.
35. Fairweather-Tait SJ, Teucher B. Iron and calcium bioavailability of fortified foods and dietary supplements. Nutr Rev 2002;60:360-7.
36. Pauline M, Verghese ST, Srinivasu BY, Bose B, Thomas T, Mandal AK, *et al*. Effect of ascorbic acid rich, micro-nutrient fortified supplement on the iron bioavailability of ferric pyrophosphate from a milk based beverage in Indian school children. Asia Pac J Clin Nutr 2018;27:792-6.
37. Mladenka P, Macakova K, Krcmov LK, Javorsk L, Carazo A, Protti M, *et al*. Vitamin K-sources, physiological role, kinetics, deficiency, detection, therapeutic use, and toxicity. Nutr Rev 2021;80:677-98.
38. Abrams SA, Chen Z, Hawthorne KM. Magnesium metabolism in 4-year-old to 8-year-old children. J Bone Mineral Res 2014;29:118-22.
39. Abrams SA, Atkinson SA. Calcium, magnesium, phosphorus and Vitamin D fortification of complementary foods. J Nutr 2003;133:2994S-9S.
40. Du X, Zhu K, Trube A, Zhang Q, Ma G, Hu X, *et al*. School-milk intervention trial enhances growth and bone mineral accretion in Chinese girls aged 10-12 years in Beijing. Br J Nutr 2004;92:159-68.
41. Debnath S, Mondal N, Sen J. Percent of body fat, fat-mass, fat-free mass and assessment of body composition among rural school-going children of Eastern-India. Anthropological Rev 2018;81:158-73.

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SUPPLEMENTRY TABLE

Table S1: Parameters altered to benchmark the Child growth model

Parameters	Biological Significance
Specific Metabolic rates	Mass-specific metabolic rate, the rate at which we consume energy per gram of body weight and size.
Digestibility factors of carbohydrate, protein and fat	Depends on the age, food intake and metabolic health.

Table S2: Nutrient composition of the oral nutrition supplement (ONS) (Danone Nutricia AptaGrow)

Nutrients	Quantity		
	Per 100 g	Per 30 g	30 g ONS in 200 mL toned milk*
Energy (Kcal)	363	109	229
Protein (g)	14	4.2	10.7
Carbohydrates (g)	76.5	23	32.6
Fat (g)	1.0	0.3	6.7
Fructo-oligosaccharides (g)	0.5	0.15	0.2
Galacto-oligosaccharides (g)	4.8	1.44	1.4
Docosahexaenoic acid (DHA) (mg)	40	12	12
Taurine (mg)	30	9	9
Choline (mg)	40	12	12
Carnitine (mg)	11	3.3	3.3
Vitamin A (mcg)	560	168	232
Vitamin D (mcg)	8.5	2.55	4.5
Vitamin E (mg)	14	4.3	4.6
Vitamin K2 (mcg)	16	4.8	4.8
Vitamin C (mg)	45	13.5	13.5
Folic acid (mcg)	70	21	21
Vitamin B12 (mcg)	1.5	0.45	1.5
Iron (mg)	7.0	2.1	2.1
Calcium (mg)	550	165	411
Phosphorus (mg)	410	123	325
Magnesium (mg)	65	19.5	43.3
Zinc (mg)	6.0	1.8	2.6

*For analysis, values of 30g ONS in 200 mL toned milk were used