**SUPPLEMENTARY MATERIAL**

**SUPPLEMENTARY METHODS (detailed methodology)**

**Study design**

The COGNIS study, registered at www.ClinicalTrials.gov (Identifier: NCT02094547), is a prospective, double-blind randomized clinical trial (RCT) with a nutritional intervention using a new infant formula enriched with bioactive nutrients Milk Fat Globule Membrane (MFGM) components [(10% of total protein (wt:wt)], long-chain polyunsaturated fatty acids (LC-PUFAs) [docosahexaenoic acid (DHA) and arachidonic (AA) acid], synbiotics (mix of fructooligosaccharide (FOS) and inulin (ratio 1:1), *Bifidobacterium infantis IM1* and *Lactobacillus rhamnosus LCS-*742), nucleotides, sialic acid and ganglioside-enriched whey proteins*.* Primary outcome is the neurocognitive development of children up to 6 years old. Secondary outcomes include infant growth, nutritional patterns, physical activity, microbiota composition and function, digestive tolerance, infectious and allergic events, glucose homeostasis and fatty acid status, and sleep quality and duration. Infant participants meeting eligibility criteria were included in the study.

The COGNIS study has been performed according to the Declaration of Helsinki II Principles (1,2), and the project and protocols were approved by the Research Bioethical Committee from the University of Granada (Spain), and the Bioethical Committees for Clinical Research of San Cecilio University Clinical and Mother-Infant Hospitals of Granada (Spain). All families were informed about procedures and a signed written informed consent was obtained from each parent or legal guardian before involving each child in the study.

**Setting**

* **Participants**

A total of 170 infants (see inclusion criteria below) were included in the COGNIS study between 0-2 months (maximum first 30 days of exclusive breastfeeding, followed by exclusive or >70% daily intake formula) to receive a standard infant formula (SF) or an experimental formula (EF). Moreover, 50 infants who were exclusively breastfed (BF) for at least 2 months were recruited from 0–6 months of age and included as control group.

**Inclusion/exclusion criteria**

Inclusion criteria: Eligible infants were healthy term infants [37-41 weeks gestational age (GA)], with adequate birth weight for GA (between 3-97 percentile), normal APGAR score (7-10) and umbilical pH ≥7.10. They must have availability to continue throughout the study period, and parents or legal guardians have signed the informed consent.

The exclusion criteria were defined as follows: infants participating in another study; infants who suffered neurological disorders *(hydrocephalus, perinatal hypoxia, intraventricular haemorrhage, neonatal meningitis, septic shock, West Syndrome,…*) or gastrointestinal disturbances (*mainly cows’ milk protein allergy/intolerance or lactose intolerance*); maternal pathological background [neurological diseases, mental illness, metabolopathies (*type 1 diabetes mellitus),* chronic diseases *(hypothyroidism*), maternal malnutrition or prenatal infections (*TORCH complex,..)*]*,* mothers who received during pregnancy or lactation drug treatments potentially harmful for neurodevelopment during pregnancy or lactation (*anxiolytics, antidepressants,…*); parents impossibility to continue through the study.

Regarding withdrawal criteria, those infants who after randomization met the following criteria were excluded from the study: infants fed with another infant formula (different from SF or EF) for a week or more; breastfed infants with formula intake >25% before 6 months; formula fed infants with human milk intakes higher than 25% beyond the 3rd month of life; any adverse event that could interfere with study follow-up, cows’ milk protein allergy/intolerance or lactose intolerance, infant formula intake rejection or neurological disorder.

**Sample size and statistical power**

Sample size was calculated before the beginning of the COGNIS study, as previously described (3).

Despite to participants drop-out at 18 months of life, statistical power was calculated to identify the validity of the results found in the current study. Statistical power was calculated for the current study applying the following equation (4): . Statistical power reached to detect a minimum difference of 0.6 SD in growth patterns was 80% at 18 months of age, enough to detect relevant differences in growth patterns between study groups.

**Recruitment and randomization**

Infants were recruited between 2010 and 2014 at the EURISTIKOS Excellence Centre for Pediatric Research, the School of Medicine, and the Mind, Brain and Behaviour Research Center (CIMCYC) at the University of Granada (Spain). Infants were also recruited from outpatient centres in the Granada province. A mathematical statistical method was applied to randomize infants into SF or EF groups (ratio 1:1).

**Intervention**

Infants were randomized to receive a standard infant formula (SF) (n=85) or an experimental infant formula (EF) (n=85). All infant formulas were provided by Laboratorios Ordesa, S.L. (Barcelona, Spain). Both infant formulas followed guidelines of the Committee on Nutrition of the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) (5), and the international and national recommendations for the composition of infant formulas. Nutritional composition of both infant formulas is shown in **Supplementary Table 1b**.

After infant randomization and inclusion in the study, parents were provided with a box with 12 cans of 400g of the corresponding infant formula, which covered infant feeding for approximately 1 month, along study duration, i.e. 18 months of infant age. Infants received initiation formula up to 6 months of age; and follow-on formula was given between 6-18 months of age.

**Growth and Dietary Intake**

Infants were followed-up at 1-2, 3, 4-depending of the time at study enrolment-, 6, 12 and 18 months of life. During the follow-up visits, and depending on subject age, different assessment procedures and data collection were carried out regarding growth and dietary intake (dietary records), as follows:

* **Growth:**

Growth measures were carried out by a trained paediatrician according anthropometric protocol; measurements were taken in triplicate, and mean was calculated. Further analyses of growth patterns were performed by a trained nutritionist.

***Anthropometric*** data included weight *(infants<2 years old, SOEHNLE Multina "Comfort 8352.01.001, max 20kg),* length *(infants<2 years old, Harpenden Infantometer Holtain Model 702, max 91.5 cm)* and head circumference (HC) *(SECA 212, max 59 cm)*. All anthropometric parameters were assessed according to the WHO growth standards 2006-2007 by sex and age (6), and calculated using WHO Anthro software package version 3.2.2 (World Health Organization, Geneva, Switzerland) (6).

The growth measurements analyses **(Supplementary Figure 1)** are described as follows:

**Level 1**: The parameter (measurement) was analysed at 1-2, 3, 4, 6, 12 and 18 months of life.

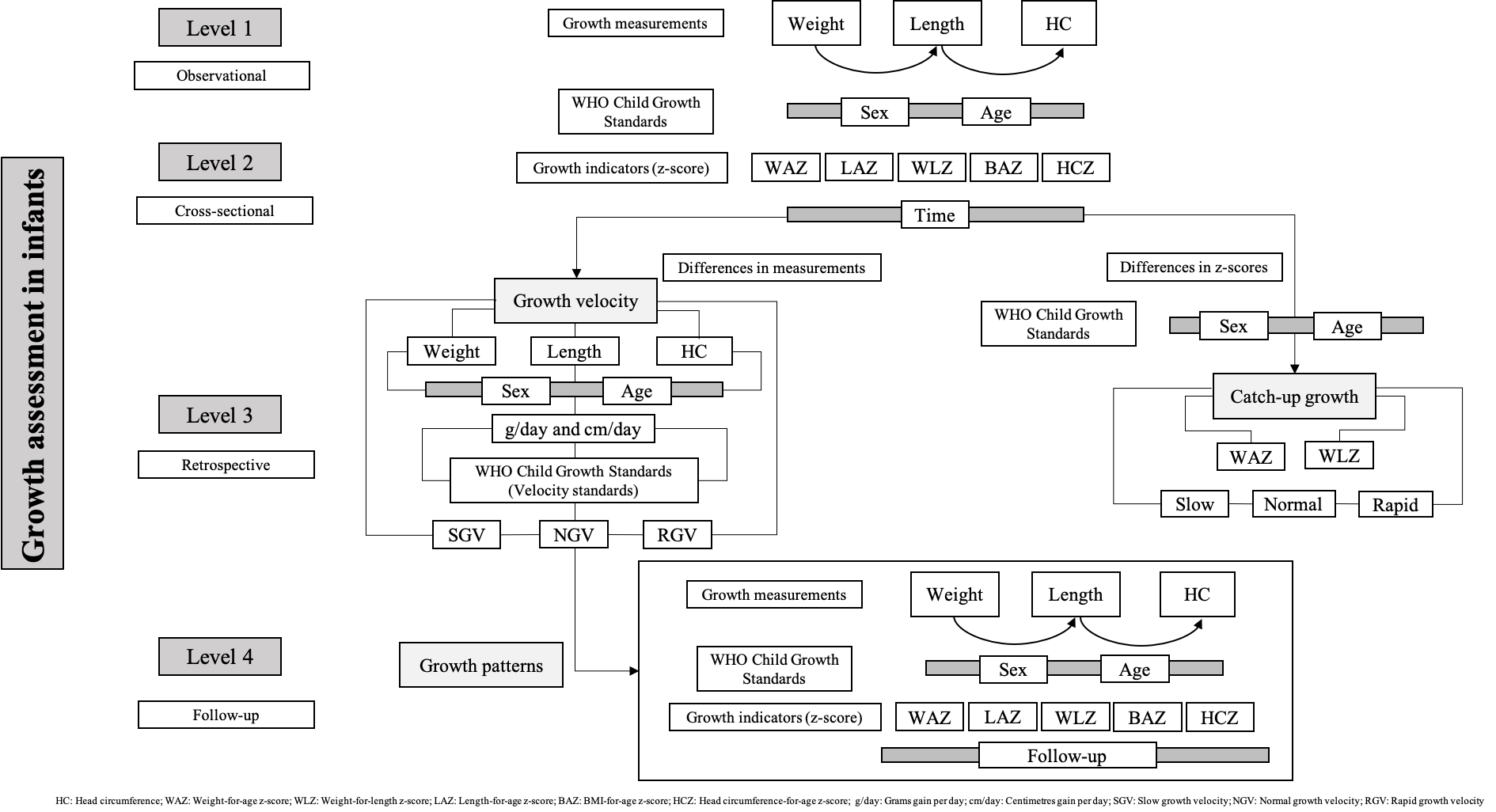
**Level 2**: The parameter of Level 1 was compared with the growth indicators, according to the current WHO Child Growth Standards (6). Weight-for-age z-score (WAZ), Weight-for-length z-score (WLZ), Length-for-age z-score (LAZ), BMI-for-age z-score (BAZ) and Head circumference-for-age z-score (HCZ) were calculated using WHO Anthro software package version 3.2.2 (World Health Organization, Geneva, Switzerland) (6). These analyses of the indicators were performed at infant´ follow-up visits.

**Level 3**: This level analysis was retrospective and involved analysis of the differences in measures (*growth velocity*) and growth indicators (*catch-up growth*), which were calculated for three different time intervals: i) from the baseline visit (formula fed infants groups) or from birth (breastfed infants) to 6 months of life, ii) from 6 to 12 months of life, and iii) from 12 to 18 months of life. This evaluation of growth along 6 months intervals:

a) *Growth velocity* was calculated according to weight gain (g/day), length gain (cm/day) and HC gain (cm/day). This data was compared using velocity standards for weight, length, and HC of the WHO growth standards presented as 6-month intervals and stratified by sex, to obtain standard deviation (SD). Growth velocity (GV) was classified as: Slow (SGV: < -1 SD), Normal (NGV: ≥ -1 SD and ≤ +1 SD) or Rapid (RGV: > +1 SD), based on the cut-off points indicated by WHO for the analysis of growth indicators and the identification of growth problems (≥ +1 SD and ≤ -1 SD) (7).

b) *Catch-up growth* was calculated based on WAZ and WLZ previously analysed in **Level 2**. Differences in z-scores were considered for three time intervals above mentioned. Afterwards, catch-up growth was classified by the differences in z-scores as follow: Slow (<-0.67), Normal (≥ -0.67 and ≤ +0.67) and Rapid (>+0.67) (8–10).

**Level 4** consisted in a follow-up analysis of the infant´ growth according to their weight growth velocity classification. The aim was to analyse the trajectory of weight, length, HC and growth indicators (WAZ, LAZ, WLZ, HCZ) up to 18 months, according to weight growth velocity up to 6 months of age. This analysis allows us to identify the growth pattern developed by each infant up to 18 months of age in our study.

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**Supplementary Figure 1: Growth measurements analyses.**

* **Dietary Intake**

Nutritional assessment and analyses of dietary patterns were carried out by a trained nutritionist.

**Feeding type:** During follow-up visits, infant’s feeding information was collected, including type of feeding prior to the study, frequency of feeding in breast fed infants or volumes of infant formula intake. The paediatrician recommended patterns of complementary feeding introduction and content, according to the Spanish Association of Paediatrics (11,12). To evaluate the effect of nutrition during the first months of life on later growth, we have also taken into account the timing of complementary feeding using dietary questionnaires.

**Dietary Intake:** Three-day dietary record was used to collect quantitative data about all the food and drinks consumed during three days, including a weekend day and two working days. DIAL software (Alce Ingeniería, Madrid, Spain) (13) was used to analyse dietary records, which converts food consumption data to nutrient intakes (macro and micronutrients).

**Estimation of breast milk/infant formula Energetic Efficiency (EE):** To analyse the EE, the average of energy and macronutrients intake of infant formula or breast milk were obtained using a three-day dietary record at 6, 12 and 18 months. Volume of breast milk intake (ml) was estimated according to the information registered in the three-day dietary record (time of feeding, frequency, volume when possible -for breast milk extraction-), infant gastric capacity and theoretical estimates (14,15). Although infants in the BF group with mixed feeding consumed infant formulas available on the market, EE analyses only consider intake of energy and macronutrients from breast milk. For the infant formula groups, the daily volume of milk (ml) was also obtained using the three-day dietary record, which reported the amount of water (ml) and powdered formula (g) for infant formula reconstitution.

Nutrients intake was calculated using DIAL software (Alce Ingeniería, Madrid, Spain) (13), which includes nutrition facts of breast milk and COGNIS infant formulas. Nutritional composition of breast milk was analysed considering it as mature human milk, and according to the components as report in the USDA National Nutrient Database for Standard Reference (16).

In dietary records, both complementary food and intake of infant formula or breast milk were reported. However, to describe the EE of infant formulas or breast milk, only daily intake of energy and macronutrients from of infant formulas or breast milk were considered.

**Supplementary References**

1. The World Medical Association Inc Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects. Ferney-Voltaire, Fr. 2008.

2. World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects. (2013). *JAMA* **310**, 2191.

3. Nieto-Ruiz, García-Santos, Bermúdez, et al. (2019) Cortical Visual Evoked Potentials and Growth in Infants Fed with Bioactive Compounds-Enriched Infant Formula: Results from COGNIS Randomized Clinical Trial. *Nutrients* **11**, 2456.

4. Martín Andrés A & Luna del Castillo J de D (2004) *Bioestadística para las ciencias de la salud*. Madrid: Norma-Capitel.

5. Koletzko B, Baker S, Cleghorn G, et al. (2005) Global Standard for the Composition of Infant Formula: Recommendations of an ESPGHAN Coordinated International Expert Group: *J. Pediatr. Gastroenterol. Nutr.* **41**, 584–599.

6. World Health Organization (WHO) (2006) The WHO Child Growth Standards. http://www.who.int/childgrowth/standards/en/.

7. World Health Organization (2008) *Training Course on Child Growth Assessment*. WHO. Geneva.

8. Ong KK, Ahmed ML, Emmett PM, et al. (2000) Association between postnatal catch-up growth and obesity in childhood: prospective cohort study. *BMJ* **320**, 967–971.

9. Stettler N, Zemel BS, Kumanyika S, et al. (2002) Infant weight gain and childhood overweight status in a multicenter, cohort study. *Pediatrics* **109**, 194–199.

10. Ong K & Loos R (2006) Rapid infancy weight gain and subsequent obesity: Systematic reviews and hopeful suggestions. *Acta Paediatr.* **95**, 904–908.

11. Lázaro Almarza & Martín Martínez (2010) Alimentación del lactante sano. *Protoc. Diagnóstico Ter. Gastroenterol. Hepatol. Nutr. Pediátrica SEGHNP-AEP 2010*, 311–320.

12. Hernández Aguilar MT & Aguayo Maldonado J (2005) La lactancia materna. Cómo promover y apoyar la lactancia materna en la práctica pediátrica. Recomendaciones del Comité de Lactancia de la AEP. *An. Pediatría* **63**, 340–356.

13. Ortega RM, López-Sobaler AM, Andrés P, et al. (2015) *DIAL software for assessing diets and food calculations*. Departamento de Nutrición (UCM) y Alce Ingeniería, S.L.

14. Dewey KG & Brown KH (2003) Update on Technical issues concerning Complementary Feeding of Young Children in Developing Countries and Implications for Intervention Programs. *Food Nutr. Bull.* **24**, 5–28.

15. Kent JC (2006) Volume and Frequency of Breastfeedings and Fat Content of Breast Milk Throughout the Day. *Pediatrics* **117**, e387–e395.

16. United States Department of Agriculture (2018) USDA Food Composition Databases.

**SUPPLEMENTARY RESULTS**

**Supplementary Table 1a. Standard and Experimental Infant Formula, and Breast Milk Nutrition Facts per 100 ml.**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Standard Formula (SF)** | | **Experimental Formula (EF)** | | **Breast milk**  **(BF)1** |
|  | **Initiation** | **Follow-on** | **Initiation** | **Follow-on** |
| **Energy** (kcal/100 ml) | 69 | 70 | 68 | 69 | 70 |
| **Protein** (g/100 ml) | 1.35 | 1.80 | 1.35 | 1.80 | 1.03 |
| **Fat (Lipids)** (g/100 ml) | 3.50 | 3.20 | 3.50 | 3.20 | 4.38 |
| **Carbohydrates** (g/100 ml) | 7.97 | 8.50 | 7.56 | 8.10 | 6.89 |

1From USDA Food Composition Databases. 01107; Milk, human, mature, fluid, 2018 (United States Department of Agriculture (2018) USDA Food Composition Databases).

**Supplementary Table 1b. Nutritional composition of the Standard (SF) and Experimental (EF) Infant Formulas used in the COGNIS study**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Standard Formula (SF)** | | **Experimental Formula (EF)** | |
|  | **Initiation** | **Follow-on** | **Initiation** | **Follow-on** |
|  | 100 ml (13.5%) | 100 ml (14.5%) | 100 ml (13.5%) | 100 ml (14.5%) |
| **Energy** (kcal/kJ) | 69/288 | 70/294 | 68/285 | 69/290 |
| **Proteins** (g) | 1.35 | 1.8 | 1.35 | 1.8 |
| Casein/whey (%) | 40/60 | 50/50 | 40/60 | 50/50 |
| **Carbohydrates** (g) | 7.97 | 8.5 | 7.56 | 8.1 |
| Lactose (g) | 7.17 | 7.2 | 6.82 | 7.3 |
| Maltodextrin (g) | 0.8 | 1.3 | 0.7 | 0.8 |
| **Fat** (g) | 3.5 | 3.2 | 3.5 | 3.2 |
| LA (mg) | 579 | 517 | 569 | 517 |
| ALA (mg) | 49 | 45 | 49 | 45 |
| ARA (mg) | - | - | 15.8 | 10.2 |
| DHA (mg) | - | - | 11.2 | 10.2 |
| **Gangliosides** (mg/L) | 1.5 | 1.5 | 9 | 9 |
| **Sialic acid** (mg/L) | 82 | 80 | 105 | 105 |
| **MFGM-10** (wt/wt) | - | - | 10% | 10% |
| **Nucleotides** (mg) | - | - | 2.92 | 2.94 |
| Cytidine-5'-Monophosphate (mg) | - | - | 1.09 | 1.12 |
| Uridine-5'-Monophosphate (mg) | - | - | 0.88 | 0.9 |
| Adenosine-5'-Monophosphate (mg) | - | - | 0.41 | 0.41 |
| Guanosine-5'-Monophosphate (mg) | - | - | 0.27 | 0.26 |
| Inosine-5'-Monophosphate (mg) | - | - | 0.27 | 0.26 |
| **Prebiotics** |  |  |  |  |
| *FOS: Inulin 1:1* | - | - | 0.4 | 0.4 |
| **Probiotics** |  |  |  |  |
| *Bifidobacterium L. infantis* CECT7210 *(Bifidobacterium infantis* IM1*)* | - | - | 1x10^7 cfu/g | 1x10^7 cfu/g |
| *Lactobacillus rhamnosus* LCS-742 | - | - | 1x10^7 cfu/g | 1x10^7 cfu/g |

Initiation formula: Up to 6 months of age. Follow-on formula: between 6-18 months of age. ARA: Arachidonic acid; cfu: colony forming unit; DHA: Docosahexaenoic acid; FOS: Fructooligosaccharides; LA: Linoleic acid; MFGM: milk fat globule membrane; ALA: α-Linolenic acid. Power diluted 13.5% (13.5 g infant formula made up to 100 ml with water); Power diluted 14.5% (14.5 g infant formula made up to 100 ml with water).

**Supplementary Table 2. Interaction between growth velocity up to 6 months and study groups.**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Study group (group effect)** | **Weight growth velocity up to 6 months of life (weight growth velocity effect)** | **Interaction between weight growth velocity and study group** |
| **Variables** | ***P*** | ***P*** | ***P*** |
| Weight 6 months | 0.534 | **0.000** | 0.137 |
| Length 6 months | 0.910 | **0.000** | 0.283 |
| HC 6 months | 0.264 | **0.005** | 0.206 |
| WLZ 6 months | 0.426 | **0.000** | 0.712 |
| WAZ 6 months | 0.832 | **0.000** | 0.432 |
| LAZ 6 months | 0.684 | **0.000** | 0.600 |
| HCZ 6 months | 0.353 | **0.000** | 0.654 |
| Weight 12 months | 0.314 | **0.000** | 0.240 |
| Length 12 months | 0.422 | **0.000** | 0.871 |
| HC 12 months | 0.754 | 0.053 | 0.169 |
| WLZ 12 months | 0.222 | **0.000** | 0.200 |
| WAZ 12 months | 0.268 | **0.000** | 0.277 |
| LAZ 12 months | 0.568 | **0.000** | 0.981 |
| HCZ 12 months | 0.885 | **0.024** | 0.254 |
| Weight 18 months | 0.588 | **0.000** | 0.314 |
| Length 18 months | 0.916 | **0.000** | 0.525 |
| HC 18 months | 0.967 | 0.139 | 0.348 |
| WLZ 18 months | 0.317 | **0.000** | 0.354 |
| WAZ 18 months | 0.389 | **0.000** | 0.316 |
| LAZ 18 months | 0.928 | **0.000** | 0.654 |
| HCZ 18 months | 1.000 | 0.102 | 0.291 |

HC: Head circumference; WAZ: Weight-for-age z-score; WLZ: Weight-for-length z-score; LAZ: Length-for-age z-score; HCZ: Head circumference-for-age z-score. Bold: *P-values* < 0.05.

**Supplementary Table 3. Growth patterns up to 18 months of life, according to weight growth velocity up to 6 months of life by feeding group.**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | **6 months old** | | | | | | | | | **12 months old** | | | | | | | | | **18 months old** | | | | | | | | |
|  |  | **Slow** | ***P*** | ***Padj*** | **Normal** | ***P*** | ***Padj*** | **Rapid** | ***P*** | ***Padj*** | **Slow** | ***P*** | ***Padj*** | **Normal** | ***P*** | ***Padj*** | **Rapid** | ***P*** | ***Padj*** | **Slow** | ***P*** | ***Padj*** | **Normal** | ***P*** | ***Padj*** | **Rapid** | ***P*** | ***Padj*** |
| **Weight (kg)** | SF | 6.86±0.69 | 0.676 | 0.350 | 7.56±0.60a | **<0.001** | **0.025** | 8.46±0.86 | 0.754 | 0.982 | 8.10±0.98 | 0.309 | 0.241 | 9.59±0.82 | 0.092 | 0.212 | 10.69±1.00 | 0.912 | 0.810 | 9.96±1.02 | 0.378 | 0.317 | 10.86±0.95 | 0.353 | 0.413 | 11.91±1.11 | 0.650 | 0.921 |
| EF | 6.54±0.62 | 7.54±0.61a,b | 8.50±0.88 | 8.25±0.80 | 9.63±0.83 | 10.68±1.08 | 9.70±0.92 | 11.02±0.97 | 12.06±1.14 |
| BF | 7.33±0.75 | 7.11±0.61b | 8.44±0.90 | 9.62±1.11 | 9.20±0.89 | 10.44±1.12 | 10.99±1.11 | 10.63±0.98 | 11.96±1.16 |
| **Length (cm)** | SF | 62.74±2.11 | 0.728 | 0.100 | 66.24±1.84a | **0.003** | **0.041** | 66.78±2.63 | 0.899 | 0.991 | 71.54±4.21 | 0.918 | 0.453 | 74.85±2.25 | **0.032** | 0.051 | 75.89±2.40 | 0.775 | 0.633 | 76.79±3.23 | 0.809 | 0.123 | 80.76±2.65 | 0.067 | 0.103 | 82.45±2.82 | 0.943 | 0.992 |
| EF | 63.38±1.91 | 66.20±1.89a,b | 66.69±2.70 | 71.45±3.44 | 74.60±2.27 | 75.50±2.59 | 77.15±2.93 | 81.80±2.72 | 82.50±2.90 |
| BF | 67.30±2.30 | 64.95±1.90b | 66.80±2.75 | 75.81±4.81 | 73.19±2.44 | 74.98±2.69 | 82.96±3.53 | 80.07±2.74 | 82.59±2.96 |
| **HC (cm)** | SF | 43.74±1.61 | 0.779 | 0.323 | 43.28±1.14a,b | **0.001** | **0.008** | 44.15±1.34 | 0.188 | 0.491 | 46.18±2.24 | 0.649 | 0.489 | 45.96±1.21 | 0.051 | 0.106 | 47.12±1.42 | 0.431 | 0.336 | 48.06±2.14 | 0.799 | 0.295 | 47.14±1.30a | 0.077 | **0.031** | 48.13±1.44 | 0.579 | 0.734 |
| EF | 42.21±1.46 | 43.76±1.17a | 43.92±1.37 | 44.91±1.83 | 46.62±1.23 | 46.48±1.54 | 46.07±1.93 | 48.08±1.34b | 48.05±1.48 |
| BF | 43.51±1.76 | 42.63±1.17b | 43.51±1.40 | 46.78±2.55 | 45.99±1.32 | 46.45±1.60 | 48.09±2.34 | 47.39±1.34a,b | 47.69±1.51 |
| **WAZ** | SF | -1.32±0.51 | 0.870 | 0.662 | -0.19±0.67 | **0.016** | 0.220 | 0.84±0.70 | 0.918 | 0.997 | -1.32±0.93 | 0.343 | 0.324 | 0.14±0.80 | 0.420 | 0.449 | 1.04±0.77 | 0.891 | 0.996 | -0.78±0.97 | 0.427 | 0.545 | 0.12±0.76 | 0.870 | 0.891 | 0.90±0.71 | 0.727 | 0.996 |
| EF | -1.09±0.46 | -0.26±0.69 | 0.85±0.72 | -0.88±0.84 | 0.15±0.83 | 1.05±0.79 | -0.78±0.88 | 0.13±0.78 | 0.93±0.73 |
| BF | -0.88±0.55 | -0.52±0.69 | 0.84±0.73 | 0.09±1.02 | -0.06±0.83 | 1.02±0.80 | 0.07±1.07 | 0.03±0.78 | 0.92±0.75 |
| **LAZ** | SF | -2.27±0.59a | 0.493 | **0.036** | -0.35±0.84 | 0.186 | 0.338 | -0.02±0.98 | 0.994 | 0.967 | -2.26±0.99 | 0.968 | 0.104 | -0.16±0.97 | 0.185 | 0.194 | 0.25±0.89 | 0.835 | 0.751 | -1.75±1.25 | 0.746 | 0.262 | -0.36±0.96 | 0.334 | 0.410 | 0.19±0.80 | 0.957 | 0.927 |
| EF | -1.19±0.54a,b | -0.39±0.86 | -0.08±1.01 | -1.49±0.89 | -0.25±1.00 | 0.14±0.91 | -1.55±1.13 | -0.16±0.99 | 0.11±0.82 |
| BF | -0.45±0.65b | -0.70±0.87 | 0.02±1.03 | 0.08±1.08 | -0.67±1.00 | -0.02±0.93 | 0.12±1.37 | -0.56±0.99 | 0.22±0.84 |
| **WLZ** | SF | 0.16±0.60 | 0.659 | 0.281 | 0.12±0.82 | 0.227 | 0.774 | 1.24±0.78 | 0.879 | 0.968 | -0.30±0.90 | 0.403 | 0.943 | 0.30±0.78 | 0.790 | 0.966 | 1.24±0.81 | 0.990 | 0.924 | 0.08±0.74 | 0.486 | 0.977 | 0.39±0.72 | 0.839 | 0.867 | 1.11±0.74 | 0.683 | 0.952 |
| EF | -0.34±0.54 | 0.05±0.84 | 1.27±0.80 | -0.10±0.81 | 0.36±0.80 | 1.28±0.83 | -0.01±0.67 | 0.29±0.74 | 1.18±0.76 |
| BF | -0.81±0.65 | -0.05±0.84 | 1.19±0.82 | -0.07±0.98 | 0.33±0.80 | 1.36±0.85 | -0.06±0.81 | 0.40±0.75 | 1.10±0.78 |
| **HCZ** | SF | 0.32±0.81 | 0.977 | 0.731 | 0.29±0.78a,b | **0.031** | **0.034** | 1.05±0.87 | 0.204 | 0.377 | 0.42±1.13 | 0.632 | 0.663 | 0.31±0.87 | 0.153 | 0.144 | 0.99±0.98 | 0.436 | 0.620 | 0.68±1.22 | 0.789 | 0.401 | 0.17±0.82a | 0.066 | **0.038** | 0.91±0.96 | 0.621 | 0.685 |
| EF | -0.13±0.73 | 0.63±0.80a | 0.83±0.90 | -0.15±1.02 | 0.76±0.89 | 0.75±1.00 | -0.35±1.11 | 0.74±0.85b | 0.75±0.99 |
| BF | -0.03±0.89 | 0.00±0.80b | 0.56±0.91 | 0.45±1.24 | 0.36±0.89 | 0.64±1.02 | 0.52±1.34 | 0.52±0.85a,b | 0.58±1.01 |

Data are presented as estimated marginal means±SD. *P-value* was obtained by ANOVA; *Padj* was obtained by ANCOVA for the group differences using univariate general linear model, including the effects of the following potential confounders: maternal age, height and IQ. Bold: *P-values* < 0.05. Values not sharing the same sufﬁx (ab) were significantly different in Bonferroni *post hoc* test. SF: Standard infant formula; EF: Experimental infant formula; BF: Breastfed infants. HC: Head circumference; WAZ: Weight-for-age z-score; LAZ: Length-for-age z-score; WLZ: Weight-for-length z-score, HCZ: Head circumference-for-age z-score; IQ: Intelligence quotient.

**Supplementary Table 4. Energetic efficiency analysis up to 18 months of age by feeding group.**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Group** | **6 months old** | ***P*** | ***Padj*** | **12 months old** | ***P*** | ***P adj*** | **18 months old** | ***P*** | ***P adj*** |
| **Weight gain g/100 kcal** | SF | 2.40±0.75 | 0.136 | 0.124 | 1.26±0.37a | 0.334 | **0.049‡** | 0.65±0.23 | 0.938 | 0.411 |
| EF | 2.25±0.77 | 1.22±0.37a,b | 0.67±0.23 |
| BF | 2.05±0.80 | 1.00±0.37b | 0.56±0.24 |
| **Weight gain g/g protein** | SF | 1.22±0.42a | **0.006** | **0.003** | 0.49±0.15a | **<0.001** | **<0.001**‡ | 0.25±0.10a | **0.019** | **<0.001** |
| EF | 1.12±0.43a | 0.47±0.15a | 0.26±0.10a |
| BF | 1.46±0.45b | 0.72±0.15b | 0.40±0.10b |
| **Weight gain g/g carbohydrates** | SF | 0.21±0.07 | 0.698 | 0.801 | 0.10±0.03 | 0.475 | 0.990‡ | 0.05±0.02 | 0.314 | 0.703 |
| EF | 0.20±0.07 | 0.10±0.03 | 0.06±0.02 |
| BF | 0.21±0.07 | 0.10±0.03 | 0.06±0.02 |
| **Weight gain g/g lipids** | SF | 0.47±0.14a | **<0.001** | **<0.001** | 0.28±0.08a | **<0.001** | **<0.001**‡ | 0.14±0.05a | 0.070 | **0.007** |
| EF | 0.44±0.14a | 0.27±0.08a | 0.15±0.05a |
| BF | 0.33±0.15b | 0.16±0.08b | 0.09±0.05b |
| **Length gain mm/100 kcal** | SF | 0.082±0.029 | 0.612 | 0.083 | 0.053±0.013 | 0.408 | 0.094‡ | 0.030±0.012 | 0.330 | 0.190 |
| EF | 0.090±0.030 | 0.051±0.015 | 0.033±0.007 |
| BF | 0.074±0.030 | 0.045±0.016 | 0.029±0.010 |
| **Length gain mm/g protein** | SF | 0.042±0.014a | 0.126 | **0.023** | 0.021±0.007a | **<0.001** | **<0.001**‡ | 0.012±0.006a | **<0.001** | **<0.001** |
| EF | 0.045±0.015a,b | 0.020±0.008a | 0.013±0.007a |
| BF | 0.052±0.018b | 0.032±0.008b | 0.021±0.003b |
| **Length gain mm/g carbohydrates** | SF | 0.007±0.000 | 0.446 | 0.169 | 0.004±0.000 | 0.204 | 0.496‡ | 0.002±0.000 | 0.110 | 0.840 |
| EF | 0.008±0.000 | 0.004±0.000 | 0.003±0.000 |
| BF | 0.008±0.000 | 0.005±0.000 | 0.003±0.000 |
| **Length gain mm/g lipids** | SF | 0.054±0.020 | 0.209 | 0.409‡ | 0.012±0.000a | **<0.001** | **<0.001**‡ | 0.007±0.000a | **0.015** | **0.002** |
| EF | 0.048±0.020 | 0.011±0.000a | 0.007±0.000a,b |
| BF | 0.054±0.020 | 0.007±0.004b | 0.005±0.003b |

Data are presented as estimated marginal means±SD. *P*-*value* was obtained by ANOVA; *Padj* was obtained by MANCOVA for group differences using multivariate general linear model, including the following confounders: maternal age, height and IQ. At 6-month of age, analysis was additionally adjusted by volume intake (ml/day) infant formula or breast milk. Values not sharing the same sufﬁx (ab) were significantly different in Bonferroni *post hoc* test. ‡P*adj* corresponds to log‐transformed variable. Bold: *P-value <0.05.*SF: Standard infant formula; EF: Experimental infant formula; BF: Breastfed infants; IQ: Intelligence quotient.