Growth patterns and breast milk/infant formula energetic efficiency in healthy infants up to 18 months of life: the COGNIS study

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Abstract

Type of feeding during early life influences growth trajectory and metabolic risk at later ages. Modifications in infant formula composition have led to evaluate their effects on growth and energetic efficiency (EE) compared with breast-feeding. Main goal was to analyse type of feeding potential effects during first months of life, plus its EE, on growth patterns in healthy formula fed (standard infant formula (SF) *vs.* experimental infant formula enriched with bioactive nutrients (EF)) and breastfed (BF) infants participating in the COGNIS RCT (www.ClinicalTrials.gov, Identifier: NCT02094547) up to 18 months of age. Infants follow-up to 18 months of age (*n* 141) fed with a SF (*n* 48), EF(*n* 56), or BF (*n* 37), were assessed for growth parameters using WHO standards. Growth velocity (GV) and catch-up were calculated to identify growth patterns. EE of breast milk/infant formula was also estimated. Infants' growth at 6 months showed higher length and lower head circumference gains in SF and EF infants than BF infants. Both weight-for-length and weight-for-age catch-up growth showed significant differences in formula fed groups compared with the BF. No significant differences in GV or catch-up were found at 6–12 and 12–18 months. Regarding EE, infant formula groups showed significantly lower weight and length gains/g of milk protein, and higher weight and length gains/g of milk lipids, than the BF infants. GV during first 6 months, which may be influenced by feeding, seems to be the main predictor of subsequent growth trajectory. Breast-feeding may have positive effects on growth programming due to its nutrients' EE.

Key words: Growth patterns: Energetic efficiency: Infant formula: Bioactive nutrients: Breast milk

Type of feeding after birth has been associated with growth velocity (GV) during the first years of life and may determine growth during childhood and adolescence. Both weight gain during the first 2 years of life and differences in weight-for-age *z*-score (WAZ) indicator could define child growth pattern[1,2]. Different authors have described a rapid growth pattern in infants associated with higher risk of obesity[1,3–6], type 2 diabetes and CVD later on[7–10].

The WHO recommends exclusive breast-feeding (BF) during the first 6 months of life, continuing at least until 24 months of age along with complementary feeding[11,12]. Infant formulas intent to promote an adequate growth, neurodevelopment and health programming in infants, when breast-feeding is not possible[13]. However, feeding with infant formulas has been shown to increase weight gain and BMI during the first year of life[14,15], compared with breast milk.

During last years, infant formulas have been modified and enriched with bioactive ingredients similar to those present in human milk to provide the necessary amount of energy and nutrients to reach an optimal growth[16]. Both the protein and lipid fractions of bovine milk fat globule membrane[17–20], long-chain PUFAs (arachidonic acid, DHA, etc.)[21,22], synbiotics (probiotics and prebiotics)[23,24], sialic acid and milk oligosaccharides[25,26] have been added to infant formulas as an alternative to narrow the nutritional and functional gap compared with breast milk. Furthermore, protein content modification[27] and infant formula supplementation with different nutrients have been studied to identify their effects on energetic efficiency (EE)[28,29], growth, development and immune function compared with breast-feeding[13,30].

To date, numerous studies have been focused on the effects of enriched infant formulas on growth rates, obesity risk associated with protein intake at early ages and benefits of the fatty acid profile or other nutrients in childhood neurodevelopment[12,31–33]. Nevertheless, there is insufficient scientific evidence about the effect of bioactive compounds-enriched infant formulas on infant growth trajectory[30]. Having in mind these considerations, the present study was aimed to analyse the potential effects of the type of feeding during the first months of life, as well as its EE, on growth patterns in healthy formula fed (standard *v.* enriched infant formula) and breastfed (BF) infants up to 18 months of age.

Methods

The present study was carried out following the updated Declaration of Helsinki Principles[34,35], the Good Clinical Practice recommendations of the ECC (document 111/3976/88 July 1990) and Spanish Royal Decree 561/1993 on clinical trials. All procedures involved in the COGNIS study were approved by the Research Bioethical Committee from the University of Granada, as well as the Bioethical Committees for Clinical Research of San Cecilio and Mother-Infant Hospitals of Granada. All families were informed about protocols and a signed written consent was obtained from each parent or legal guardian before involving each child in the study.

Study design and subjects

The COGNIS study (registered at www.ClinicalTrials.gov, Identifier: NCT02094547) is a prospective, double-blind randomised clinical trial (RCT) with a nutritional intervention using a new infant formula enriched with bioactive nutrients such as milk fat globule membrane components (10 % of total protein (wt:wt)), long-chain PUFAs (DHA and arachidonic acid), synbiotics (mix of fructooligosaccharide and inulin (ratio 1:1), *Bifidobacterium infantis* IM1 and *Lactobacillus rhamnosus* LCS-742), nucleotides, sialic acid and ganglioside-enriched whey proteins.

Inclusion criteria. Eligible infants were healthy term infants (37–41 weeks gestational age), with adequate birth weight for gestational age (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.

Exclusion criteria. 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, etc.*) 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, etc.*)), mothers who received during pregnancy or lactation drug treatments potentially harmful for neurodevelopment (*anxiolytics, antidepressants, etc.*); parents impossibility to continue through the study. A detailed description of the COGNIS study can be found in online Supplementary Methods. Briefly, a total of 220 full-term infants were enrolled, 170 of them were randomised (ratio 1:1) to receive, during their first 18 months of life, either a standard infant formula (SF; *n* 85) or an experimental infant formula (EF; *n* 85) enriched with bioactive nutrients. A total of fifty exclusively breastfed (BF) infants for at least 2 months were also included as reference group. The present study involved 171 infants at 6 months (SF = 60; EF = 69; BF = 42); 152 infants at 12 months (SF = 51; EF = 63; BF = 38) and 141 infants at 18 months (SF = 48; EF = 56; BF = 37). A detailed participant flow chart from the baseline visit to 18 months of life is shown in Fig. 1.

Demographical and clinical characteristics

Baseline information about maternal and paternal age, anthropometric characteristics (BMI and height), as well as their educational level, place of residence and intelligence quotient (IQ) was obtained at study entry. Prenatal characteristics (weight gain during pregnancy, siblings, type of delivery and smoking during pregnancy) were also recorded. Data regarding weight, length and head circumference (HC) at birth were taken from clinical records.

Evaluation of infant growth patterns

To analyse the potential effects of the type of feeding on infants growth, anthropometric measurements were collected at 1–2, 3, 4, 6, 12 and 18 months of life by a trained paediatrician, following standard procedures[36]; measurements were taken in triplicate and their means were calculated. Analyses of growth patterns were performed by a trained nutritionist. A detailed description of growth measurements analyses can be found in online Supplementary Methods.

Anthropometric data included weight (SOEHNLE Multina Comfort 8352·01·001, max 20 kg), length (Harpenden Infantometer Holtain Model 702, max 91·5 cm) and HC (SECA 212, max 59 cm). All anthropometric parameters were assessed according to the current WHO Child Growth Standards by sex and age[37,38]. WAZ, weight-for-length *z*-score (WLZ), length-for-age *z*-score (LAZ), BMI-for-age *z*-score and HC-for-age *z*-score (HCZ) were calculated using WHO Anthro software package version 3.2.2 (WHO)[37].

GV was calculated according to weight, length and HC gains/d. Weight gain (g/d), length gain (cm/d) and HC (cm/d) were calculated at three different time intervals: (i) from the baseline visit (formula fed infants groups) or from birth (BF infants) to
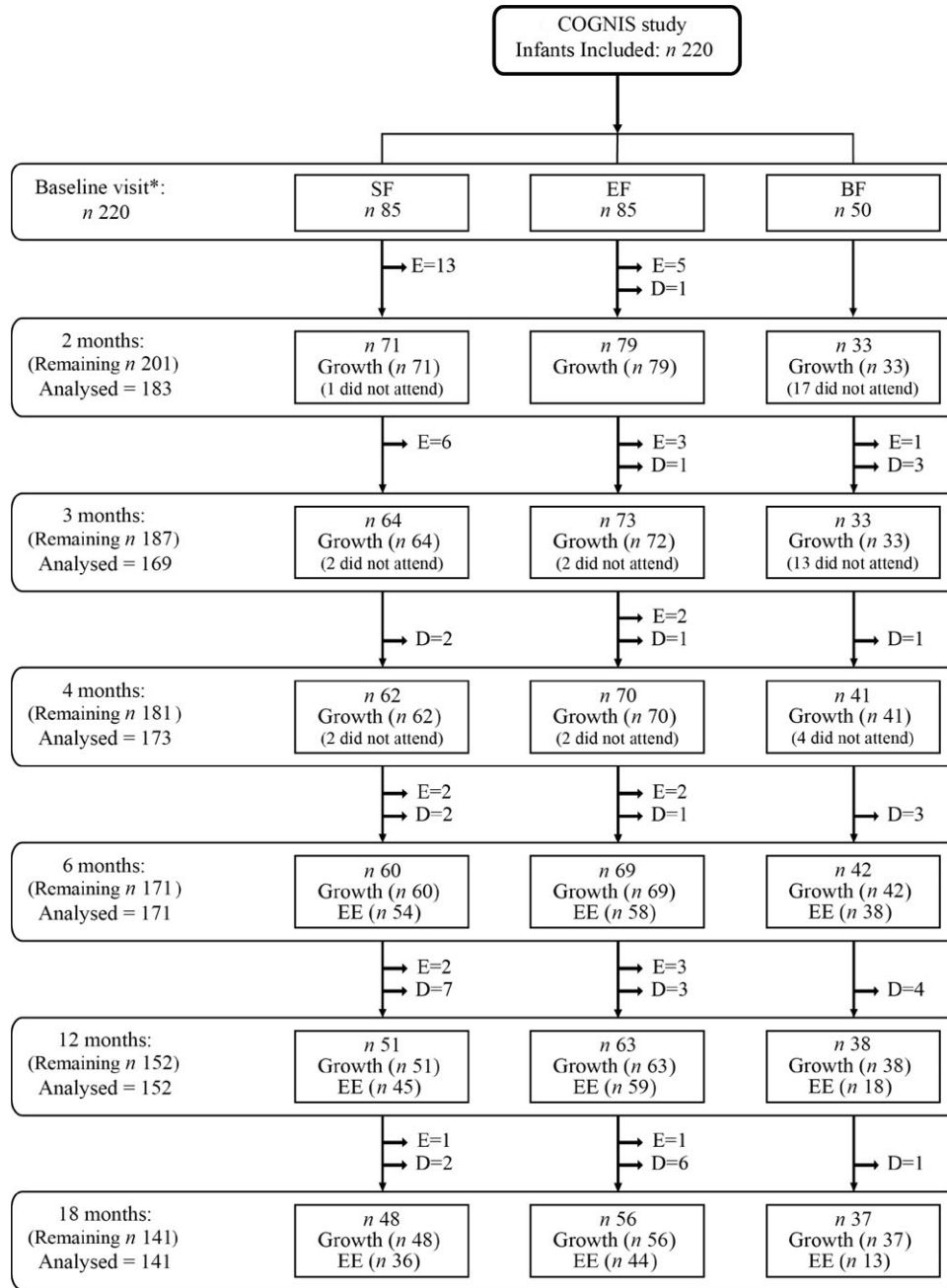
Fig. 1. Dropout rates and exclusions from the baseline visit to 18 months of age. Infants who did not show up at the follow-up visits, but remained in COGNIS study for later visits are described as 'did not attend'. SF, standard infant formula; EF, experimental infant formula; BF, breastfed infants; EE, energetic efficiency. D = drop outs and E = exclusions, as previously reported[41]. *SF and EF infants were randomised between 0 and 2 months of age; BF infants were included up to 6 months of age.

6 months of life, (ii) from 6 to 12 months of life and (iii) from 12 to 18 months of life. These data were 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 deviations (SD). GV was classified as: slow (< -1 SD), normal (≥ -1 SD and $\leq +1$ SD) or rapid ($> +1$ SD), based on the cut-off points indicated by WHO for the analysis of growth indicators and the identification of growth problems ($\geq +1$ SD and ≤ -1 SD)[36]. After this, to identify infant growth pattern developed up to 18 months of age, trajectories of weight, length, HC and

growth indicators WAZ, LAZ, WLZ and HCZ were analysed up to 18 months, according to weight GV up to 6 months of age.

Catch-up growth is defined as the variation in infant weight gain rates, which shows a significant growth to compensate from intra-uterine restriction or enhancement of growth, during the first 2 years of life[1,3]. Catch-up growth was calculated as WAZ and WLZ. Differences in z-scores were considered as the three time intervals mentioned above. Afterwards, catch-up growth was classified by the differences in z-scores as follows: slow (< -0.67), normal (≥ -0.67 and $\leq +0.67$) and rapid ($> +0.67$)[1,3].

Estimation of breast milk/infant formula energetic efficiency

This parameter is described as the increase in weight and length according to the energy and macronutrient intake (proteins, carbohydrates and lipids) per day from infant formula or breast milk[28,29]. The average of energy and macronutrients intake was obtained using a 3-d dietary record at 6, 12 and 18 months. For the infant formula groups, the daily volume of milk (ml) was reported as the amount of water (ml) and powdered formula (g) for infant formula reconstitution. Volume of breast milk intake (ml) was estimated according to infant gastric capacity and theoretical estimates for breast milk intake[39,40]. Detailed description in this regard is included in online Supplementary Methods. EE was expressed as (a) weight gain (g/d)/4184 kJ (100 kcal) of milk, (b) weight gain (g/d)/g of milk protein, (c) weight gain (g/d)/g of milk carbohydrate, (d) weight gain (g/d)/g of milk lipids, (e) length gain (mm/d)/418·4 kJ (100 kcal) of milk, (f) length gain (mm/d)/g of milk protein, (g) length gain (mm/d)/g of milk carbohydrate and (h) length gain (mm/d)/g of milk lipids[28,29].

Statistical analyses

All statistical analyses were conducted using IBM® SPSS Statistics® programme, version 22.0 (SPSS Inc.). Shapiro–Wilk and Kolmogorov–Smirnov tests, as well as visual inspection of histograms, were applied for all variables in the three study groups to check them for normality. Variables with normal distribution were presented as means and standard deviations, while non-normally distributed variables as median and interquartile range. Categorical variables were expressed as frequencies and percentages. Differences among BF, SF and EF groups were tested using ANOVA or Welch and Student *t* test for two groups, Kruskal–Wallis rank sum test for non-normally distributed variables, and χ^2 or Fisher's exact tests for categorical variables were used depending on the response variable. Interaction test between weight GV up to 6 months and the study groups was performed to identify effects on infant's growth. Relevant confounders (maternal age, height and IQ) were included in the ANCOVA and in the adjusted multivariate ANCOVA. Bonferroni corrected *post hoc* comparisons were used to identify significant group differences in pairs. $P < 0.05$ values were considered statistically significant.

Sample size was calculated before the beginning of the COGNIS study, as previously described[41]. Statistical power was calculated for the present study applying the following equation[42]:

$$n = 2\frac{(Z\alpha + Z2\beta)^2}{\delta'}.$$

Results

Background characteristics and baseline data of parents and infants participating in the COGNIS study are shown in Table 1. There were statistically significant differences between study groups with respect to maternal age, height and IQ. Mothers of BF infants were older and taller than mothers of EF infants

($P = 0.028$ and 0·005, respectively). These variables (maternal age and height) were included as confounders in further growth patterns statistical analyses. Furthermore, mothers of BF group showed higher IQ compared with the mothers of the formula fed groups (SF and EF) ($P < 0.001$); thus, IQ was also included as a confounder since it was identified as a variable that may be directly or indirectly related to growth and development and the type of feeding in infants[12,43].

Regarding newborn's characteristics, no differences were found between study groups in anthropometrics parameters at birth, including weight, length, HC and their respective *z*-scores by age (WAZ, WLZ, LAZ, BMI-for-age *z*-score and HCZ). Breast-feeding days were significantly different between the three study groups ($P < 0.001$) due to the design of the COGNIS study.

Effects of the type of feeding on anthropometric characteristics and daily growth gain in infants during their first 18 months of life

Results concerning infants' anthropometric measures are shown in Table 2. HC at 4 and 6 months was bigger in the formula fed groups compared with the BF infants in the confounders (maternal age, height and IQ) adjusted model ($P_{adj} = 0.013$; $P_{adj} = 0.004$, respectively). HCZ was also significantly higher at 4 and 6 months in the formula fed infants in comparison with those in the BF group ($P_{adj} = 0.018$; $P_{adj} = 0.008$, respectively). Moreover, length at 12 months of age was higher in the SF group than in the BF group ($P_{adj} = 0.041$) (Table 2). No significant differences were found in WAZ, WLZ, LAZ and BMI-for-age *z*-score along the COGNIS groups.

In order to estimate GV in COGNIS infants, we next evaluate weight, length and HC gains in three time intervals: (i) up to 6 months, (ii) between 6 and 12 months and (iii) between 12 and 18 months (Table 3). Infants from the formula fed groups (SF or EF) had significantly higher length gain (cm/d) ($P_{adj} = 0.015$) and lower HC gain (cm/d) ($P_{adj} = 0.001$) compared with the BF infants at 6 months of age. Between 6 and 12 months of age, the SF group presented a significantly lower HC gain compared with BF infants ($P_{adj} = 0.019$) (Table 3).

Growth velocity and catch-up growth

Infants' GV and catch-up indicators were classified as slow, normal or rapid according to the aforementioned criteria in the 'Methods' section. At 6 months, the SF group showed a lower proportion of slow length GV when compared with the BF infants ($P = 0.028$). Formula fed infants showed higher proportion of slow, and lower proportion of rapid HC GV compared with the BF infants ($P < 0.001$) (Table 4). When analysing the WAZ catch-up until 6 months of life, the formula fed groups (SF or EF) had significantly lower percentage of slow and higher percentage of rapid catch-up growth compared with the BF group ($P < 0.001$). Regarding WLZ catch-up until 6 months of life, EF and BF groups are characterised by higher proportion of normal catch-up growth compared with the SF group, although not reaching significant difference. On the other hand, the SF group showed a lower percentage of infants classified as slow catch-up growth ($P = 0.046$). No significant differences

Table 1. Parents and infants baseline characteristics by study group

	SF						EF						BF						P**
	Mean	SD	n	%	Median	Range	Mean	SD	n	%	Median	Range	Mean	SD	n	%	Median	Range	
Maternal age (years)*	30·51	6·74[a,b]					30·10	5·99[a]					32·94	5·38[b]					**0·028**
Pre-conceptional maternal BMI (kg/m²)†					24·18	21·75–27·61					23·68	21·14–27·30					23·90	21·80–26·16	0·842
Maternal height (m)*	1·61	0·06[a,b]					1·60	0·06[a]					1·63	0·06[b]					**0·005**
Maternal IQ (points)*	101·29	15·51[a]					97·47	16·02[a]					108·90	14·22[b]					**< 0·001**
Smoking during pregnancy‡			13	18·84					10	12·99					2	4·65			0·098
Weight gain during pregnancy (kg)†					7	3·5–10					6	3–9·50					6	4–9	0·781
Type of delivery‡																			
Vaginal			62	72·94					60	70·59					37	74·00			0·899
Caesarean			23	27·06					25	29·41					13	26·00			
Siblings (≥ 1)‡			52	61·20					43	50·60					22	44·00			0·128
Paternal age (years)*	32·68	6·89					33·31	7·03					35·07	5·01					0·134
Paternal BMI (kg/m²)†					27·65	24·55–30·48					26·95	24·75–29·63					27·25	24·60–29·63	0·950
Paternal height (m)*	1·74	0·06					1·73	0·06					1·75	0·07					0·436
Paternal IQ (points)†					108	96–117					102	92–111					108	99–117	0·062
Place of residence‡																			
Urban			38	44·71					28	32·94					15	30·00			0·148
Rural			47	55·29					57	67·06					35	70·00			
Newborn characteristics																			
Gestational age at birth (weeks)†					40	38–40					40	39–40					39·50	38–40·25	0·925
Sex‡																			
Boy			49	57·65					51	60·00					21	42·00			0·105
Girl			36	42·35					34	40·00					29	58·00			
Birth weight (g)*	3266·25	459·08					3347·76	486·41					3321·20	431·73					0·513
Birth length (cm)†					50	49–52					51	49–52					51	49–51·25	0·431
Birth head circumference (cm)†					35	34–35·5					34·25	34–35					35	33·25–35	0·481
Birth WAZ (z-score)*	−0·11	0·98					0·11	0·95					0·05	0·88					0·320
Birth WLZ (z-score)*	−0·67	1·06					−0·66	1·02					−0·62	1·08					0·972
Birth LAZ (z-score)†					0·46	−0·08–1·12					0·92	0·06–1·53					0·59	−0·08–1·02	0·247
Birth BAZ (z-score)*	−0·48	1·00					−0·36	1·00					−0·41	1·00					0·667
Birth HCZ (z-score)*	0·38	1·05					0·21	0·93					0·25	0·99					0·581
Breast-feeding (d)†					8	0–21					7	1–25					420	270–540	**< 0·001**

SF, standard infant formula; EF, experimental infant formula; BF, breastfed infants; IQ, intelligence quotient; WAZ, weight-for-age z-score; WLZ, weight-for-length z-score; LAZ, length-for-age z-score; BAZ, BMI-for-age z-score; HCZ, head circumference-for-age z-score.

* Mean values and standard deviations; † medians and interquartile ranges; ‡ numbers and percentages.

** P-values for overall differences between COGNIS-groups. ANOVA for normally distributed variables, Kruskal–Wallis rank-sum test for non-normal continuous variables, and χ^2 test for categorical variables. Values which do not share the same suffix (ab) were significantly different in Bonferroni post hoc test. Bold: P-value < 0·05.

Table 2. Effect of the type of feeding on anthropometric data in infants during the first 18 months of life.

		2 months				3 months				4 months				6 months				12 months				18 months			
		Mean	SD	P*	P_{adj}*	Mean	SD	P*	P_{adj}*	Mean	SD	P*	P_{adj}*	Mean	SD	P*	P_{adj}*	Mean	SD	P*	P_{adj}*	Mean	SD	P*	P_{adj}*
Weight (kg)	SF	5·19	0·65	0·894	0·814	6·02	0·75	0·966	0·936	6·74	0·84	0·851	0·255	7·89	0·93	0·092	0·078	9·94	1·16	0·230	0·271	11·22	1·21	0·459	0·566
	EF	5·19	0·67			6·00	0·76			6·76	0·86			7·77	0·95			9·80	1·20			11·26	1·22		
	BF	5·27	0·68			6·06	0·78			6·47	0·80			7·45	0·97			9·53	1·23			10·98	1·25		
Length (cm)	SF	56·54	2·19	0·819	0·886	59·62	2·29	0·873	0·897	62·45	2·28	0·297	0·564	66·43	2·27	0·078	0·064	75·12	2·64[a]	0·069	**0·041**	81·24	2·99	0·252	0·454
	EF	56·47	2·22			59·62	2·31			62·08	2·34			66·12	2·33			74·48	2·75[a,b]			81·52	3·02		
	BF	56·31	2·27			59·84	2·37			62·04	2·17			65·31	2·38			73·63	2·81[b]			80·69	3·08		
BMI (kg/m²)	SF	16·20	1·44	0·507	0·445	16·91	1·55	0·989	0·958	17·25	1·58	0·123	0·133	17·86	1·60	0·457	0·409	17·61	1·54	0·985	0·973	17·00	1·24	0·860	0·815
	EF	16·22	1·47			16·83	1·57			17·49	1·62			17·73	1·64			17·62	1·60			16·88	1·25		
	BF	16·58	1·49			16·87	1·61			16·79	1·50			17·42	1·67			17·54	1·63			16·83	1·28		
HC (cm)	SF	39·28	1·25	0·114	0·107	40·57	1·28	0·178	0·123	41·75	1·30[a]	0·330	**0·013**	43·65	1·28[a]	**0·005**	**0·004**	46·39	1·42	0·325	0·514	47·52	1·42	0·324	0·423
	EF	39·22	1·25			40·62	1·30			41·79	1·34[a]			43·62	1·31[a]			46·37	1·48			47·83	1·44		
	BF	38·72	1·28			40·06	1·33			40·99	1·24[b]			42·82	1·34[b]			46·05	1·51			47·49	1·47		
WAZ	SF	−0·43	0·87	0·589	0·718	−0·30	0·91	0·640	0·754	−0·15	0·95	0·719	0·582	0·15	0·96	0·358	0·180	0·44	1·01	0·405	0·440	0·38	0·91	0·839	0·756
	EF	−0·38	0·89			−0·36	0·92			−0·13	0·97			0·03	0·98			0·28	1·02			0·34	0·92		
	BF	−0·28	0·90			−0·21	0·94			−0·32	0·86			−0·22	1·00			0·17	1·04			0·23	0·94		
WLZ	SF	0·43	1·05	0·393	0·354	0·34	1·04	0·926	0·916	0·26	1·02	0·132	0·160	0·52	1·01	0·625	0·544	0·63	1·03	0·903	0·945	0·65	0·87	0·948	0·900
	EF	0·46	1·07			0·26	1·05			0·44	1·04			0·42	1·04			0·57	1·06			0·59	0·88		
	BF	0·75	1·09			0·32	1·08			0·03	0·92			0·28	1·06			0·58	1·07			0·56	0·90		
LAZ	SF	−0·79	0·99	0·896	0·821	−0·66	0·95	0·536	0·736	−0·44	0·95	0·512	0·575	−0·28	0·93	0·452	0·225	−0·06	1·04	0·125	0·083	−0·22	1·00	0·574	0·642
	EF	−0·74	1·00			−0·68	0·97			−0·60	0·96			−0·36	0·96			−0·30	1·06			−0·20	1·00		
	BF	−0·87	1·02			−0·52	0·99			−0·43	0·85			−0·61	0·97			−0·57	1·07			−0·40	1·03		
BAZ	SF	0·01	0·95	0·338	0·373	0·11	1·01	0·916	0·903	0·14	1·02	0·170	0·181	0·42	1·03	0·620	0·526	0·65	1·04	0·885	0·967	0·72	0·85	0·900	0·921
	EF	0·05	0·96			0·04	1·02			0·29	1·03			0·32	1·05			0·62	1·06			0·65	0·86		
	BF	0·29	0·98			0·12	1·05			−0·10	0·92			0·18	1·08			0·68	1·08			0·66	0·88		
HCZ	SF	0·34	0·87	0·163	0·054	0·30	0·87	0·332	0·091	0·36	0·87[a]	0·107	**0·018**	0·57	0·84[a]	**0·044**	**0·008**	0·57	0·92	0·621	0·420	0·44	0·90	0·469	0·512
	EF	0·34	0·87			0·32	0·87			0·41	0·88[a]			0·58	0·86[a]			0·62	0·94			0·64	0·91		
	BF	−0·08	0·89			−0·07	0·89			−0·08	0·78[b]			0·07	0·88[b]			0·36	0·96			0·49	0·92		

SF, standard infant formula; EF, experimental infant formula; BF, breastfed infants; HC, head circumference; WAZ, weight-for-age z-score; WLZ, weight-for-length z-score; LAZ, length-for-age z-score; BAZ, BMI-for-age z-score; HCZ, head circumference-for-age z-score; IQ, intelligence quotient.
* P-value was obtained from ANOVA; P_{adj} was obtained from ANOVA; P_{adj} was obtained from ANCOVA for the group differences using univariate general linear model, including the effects from the following potential confounders: maternal age, height and IQ. Bold: P-value < 0.05.
[ab] Values not sharing the same suffix were significantly different in Bonferroni post hoc test.

Table 3. Daily growth gain in infants of the COGNIS study.

		Up to 6 months†				6–12 months				12–18 months			
		Mean	SD	P^*	P_{adj}^*	Mean	SD	P^*	P_{adj}^*	Mean	SD	P^*	P_{adj}^*
Weight gain (g/d)	SF	24·17	4·72	0·184	0·215	11·29	2·95	0·999	1·000	7·26	2·49	0·882	0·986
	EF	24·23	4·81			11·27	3·02			7·34	2·51		
	BF	22·20	4·91			11·28	3·06			7·29	2·56		
Length gain (cm/d)	SF	0·09	0·02[a]	**0·008**	**0·015**	0·05	0·01	0·137	0·136	0·03	0·01	0·062	0·069
	EF	0·09	0·02[a]			0·05	0·01			0·04	0·01		
	BF	0·08	0·01[b]			0·05	0·01			0·04	0·01		
HC gain (cm/d)	SF	0·04	0·01[a]	**< 0·001**	**0·001**	0·02	0·00[a]	**0·023**	**0·019**	0·01	0·00	0·080	0·139
	EF	0·04	0·01[a]			0·02	0·00[a,b]			0·01	0·00		
	BF	0·05	0·01[b]			0·02	0·00[b]			0·01	0·00		

SF, standard infant formula; EF, experimental infant formula; BF, breastfed infants; HC, head circumference; IQ, intelligence quotient.
* P-value was obtained from ANOVA; P_{adj} 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-value < 0·05.
† Calculated from the baseline visit (formula fed infants group) or from birth to 6 months of life (breastfed infants). Data were analysed using the WHO growth velocity standards, and presented as 6-month increments from birth to 18 months and stratified by sex[38].
[a,b] Values not sharing the same suffix were significantly different in Bonferroni *post hoc* test.

were detected in the GV and catch-up growth parameters at 6–12 and 12–18 months of age (Table 4).

Growth patterns in COGNIS infants up to 18 months

Regarding interaction between GV up to 6 months and study groups (SF, EF and BF), no statistically significant results were detected in those test (P-values >0·05) (online Supplementary Table S2). This means that there is no effect of the study group in those growth parameters and indicators evaluated. Same happens to interaction between weight GV and study group. Only one factor has effect on growth: GV up to 6 months of age ($P < 0·05$), which indicates that this factor may predict subsequent growth trajectory while diet group does not. However, due to the study design, results are presented according to study group.

Growth patterns were evaluated up to 18 months of age according to the classification of weight GV up to 6 months of age visits (Fig. 2(a)–(g) and online Supplementary Table S3).

Infants with slow growth velocity. At 6 months of age, LAZ was significantly lower in the SF group (–2·27 (SD 0·59)) compared with the BF group (–0·45 (SD 0·65)) ($P_{adj} = 0·036$) (Fig. 2(e)), although the signification did not remain at later ages.

Infants with normal growth velocity. At 6 months, weight (kg) was significantly higher in the SF infants (7·56 (SD 0·60)) compared with the BF group (7·11 (SD 0·61)) ($P_{adj} = 0·025$) (Fig. 2(a)); length (cm) was significantly higher in the SF group compared with the BF group (SF: 66·24 (SD 1·84); BF: 64·95 (SD 1·90); $P_{adj} = 0·041$) (Fig. 2(b)), while HC (cm) was significantly higher in the EF group compared with the BF group (EF: 43·76 (SD 1·17); BF: 42·63 (SD 1·17); $P_{adj} = 0·008$) (Fig. 2(c)). Similarly, at 18 months of age, the EF group presented higher HC (cm) compared with the SF group (EF: 48·08 (SD 1·34); SF: 47·14 (SD 1·30); $P_{adj} = 0·031$) (Fig. 2(c)).

Regarding growth *z*-scores, at 6 months, HCZ was significantly higher in the EF group compared with the BF group (EF: 0·63 (SD 0·80); BF: 0·00 (SD 0·80); $P_{adj} = 0·034$) (Fig. 2(g)).

And at 18 months, HCZ was higher in the EF group compared with the SF group (EF: 0·74 (SD 0·85); SF: 0·17 (SD 0·82); $P_{adj} = 0·038$) (Fig. 2(g)).

Infants with rapid growth velocity. Up to 18 months, no differences in weight, length or HC, nor WAZ, LAZ, WLZ or HCZ were found according to the feeding group (Fig. 2(a)–(g) and online Supplementary Table S3).

Energetic efficiency

EE was estimated up to 18 months of age according to energy and macronutrients intake per day from breast milk or infant formula (Fig. 3). For this purpose, we first evaluated if there were differences in infant formula/breast milk volume intake per day (d) at 6, 12 and 18 months. We found that the milk volume intake (ml/d) was significantly different between the study groups at 6 months of age (SF: 683·59 (SD 255·88); EF: 696·19 (SD 217·29); BF: 843·18 (SD 242·37), $P = 0·003$); thus, this parameter (milk volume intake) was included as an additional confounder for further EE analysis.

Energetic efficiency and weight gain (g/d). Weight gain/g of milk protein at 6, 12 and 18 months of age was significantly lower in the formula fed groups (SF or EF) compared with the BF group (6 months, $P_{adj} = 0·003$; 12 months, $P_{adj} < 0·001$; 18 months, $P_{adj} < 0·001$) (Fig. 3(a) and online Supplementary Table S4). Conversely, weight gain/g of milk lipids was significantly higher in the infant formula groups compared with the BF infants (6 months, $P_{adj} < 0·001$; 12 months, $P_{adj} < 0·001$; 18 months, $P_{adj} = 0·007$) (Fig. 3(b) and online Supplementary Table S4). Furthermore, weight gain/418·4 kJ (100 kcal) of milk was significantly higher in the SF group compared with the BF infants at 12 months of age ($P_{adj} = 0·049$). However, at 6 and 18 months of age there were no significant differences. Regarding weight gain/g of milk carbohydrates, there were no significant differences between feeding groups up to 18 months (online Supplementary Table S4).

Table 4 Growth velocity and catch-up growth in infants during the first 18 months of life by COGNIS study groups.

		Up to 6 months† SF n	%	EF n	%	BF n	%	P*	6–12 months SF n	%	EF n	%	BF n	%	P*	12–18 months SF n	%	EF n	%	BF n	%	P*
Weight growth velocity	Slow	4	6·67	10	14·49	3	7·50	0·530	0	0·00	2	3·17	0	0·00	0·786	7	14·58	3	5·36	3	8·11	0·386
	Normal	37	61·66	35	50·73	24	60·00		27	52·94	30	47·62	20	52·63		28	58·34	42	75·00	25	67·57	
	Rapid	19	31·67	24	34·78	13	32·50		24	47·06	31	49·21	18	47·37		13	27·08	11	19·64	9	24·32	
Length growth velocity	Slow	8	13·33[a]	14	20·29[a,b]	15	37·50[b]	**0·028**	3	5·88	3	4·76	2	5·36	0·119	8	16·67	4	7·14	7	18·92	0·139
	Normal	37	61·67	36	52·17	21	52·50		17	33·33	31	49·21	23	60·53		30	62·50	29	51·79	19	51·35	
	Rapid	15	25·00	19	27·54	4	10·00		31	60·78	29	46·03	13	34·21		10	20·83	23	41·07	11	29·73	
HC growth velocity	Slow	23	38·33[a]	21	30·44[a]	2	6·25[b]	**<0·001**	4	7·85	7	11·12	2	5·27	0·115	10	20·83	7	12·50	5	13·51	0·153
	Normal	32	53·34	40	57·97	16	50·00		31	60·78	28	44·44	14	36·84		31	64·59	29	51·79	20	54·05	
	Rapid	5	8·33[a]	8	11·59[a]	14	43·75[b]		16	31·37	28	44·44	22	57·89		7	14·58	20	35·71	12	32·44	
WAZ Catch-up	Slow	3	5·00[a]	8	11·59[a]	13	32·50[b]	**<0·001**	1	1·96	1	1·59	0	0·00	0·772	3	6·25	2	3·57	0	0·00	0·389
	Normal	34	56·67	32	46·38	24	60·00		39	76·47	48	76·19	26	68·42		44	91·67	51	91·07	37	100·00	
	Rapid	23	38·33[a]	29	42·03[a]	3	7·50[b]		11	21·57	14	22·22	12	31·58		1	2·08	3	5·36	0	0·00	
WLZ Catch-up	Slow	11	18·33[a]	15	21·74[a,b]	16	41·02[b]	**0·046**	7	13·73	8	12·70	3	7·89	0·211	7	14·58	7	12·50	4	10·81	0·672
	Normal	32	53·34	34	49·28	19	48·72		38	74·51	39	61·90	23	60·53		38	79·17	43	76·79	32	86·49	
	Rapid	17	28·33	20	28·98	4	10·26		6	11·76	16	25·40	12	31·58		3	6·25	6	10·71	1	2·70	

SF, standard infant formula; EF, experimental infant formula; BF, breastfed infants; HC, head circumference; WAZ, weight-for-age z-score; WLZ, weight-for-length z-score.

* χ^2 test for categorical variables. P-values are comparisons between the COGNIS-groups. Values which do not share the same suffix (a,b) are significantly different in Bonferroni *post hoc* test. Bold: P-value < 0.05. Growth velocity was classified as: slow: < -1 SD, normal: ≥ -1 SD and $\leq +1$ SD or rapid: $> +1$ SD; catch-up growth classified as follows: slow: < -0.67, normal: ≥ -0.67 and $\leq +0.67$ and rapid: $> +0.67$ (see 'Methods' section for more details).

† Calculated from the baseline visit (formula fed infants group) or from birth to 6 months of life (breastfed infants).
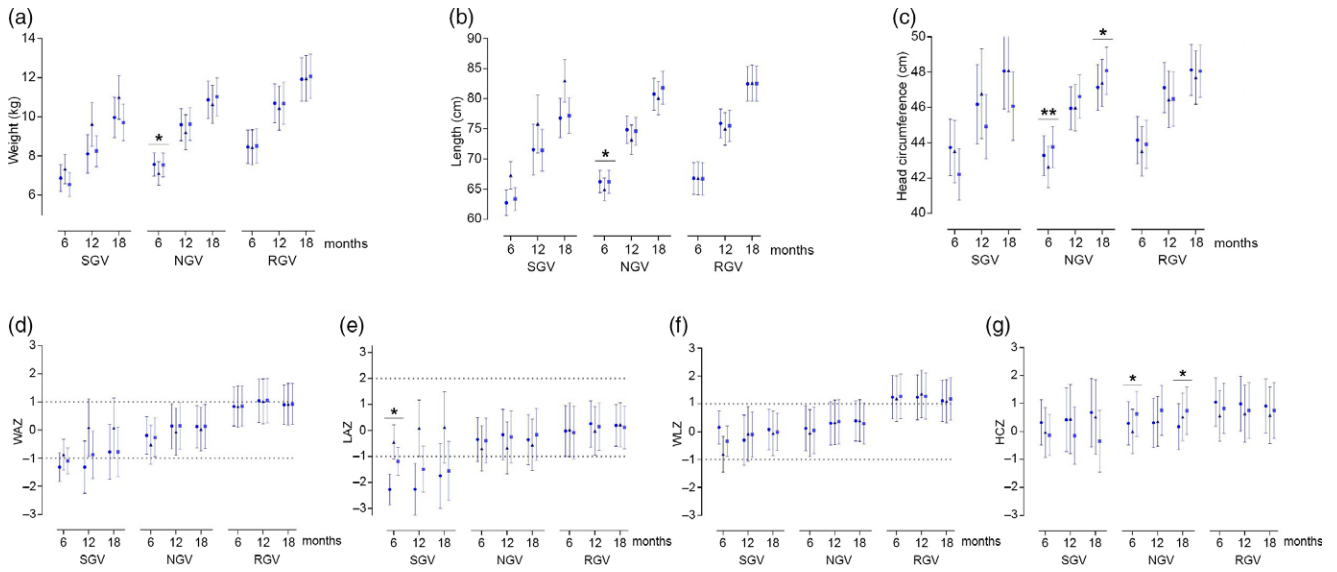
Fig. 2. Growth patterns up to 18 months of life, according to weight growth velocity up to 6 months of life by feeding group. Data are marginal mean values and standard deviations. P_{adj} was obtained by ANCOVA for the group differences using univariate general linear model, including the effects of the following potential confounders: maternal age, height and IQ. *P_{adj}-values < 0·05 and **P_{adj}-values < 0·01. SGV, slow growth velocity; NGV, normal growth velocity; RGV, rapid growth velocity; 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. Dotted lines indicate normal growth according to WHO cut-off points[37]. ●, SF; ▲, BF; ■, EF.
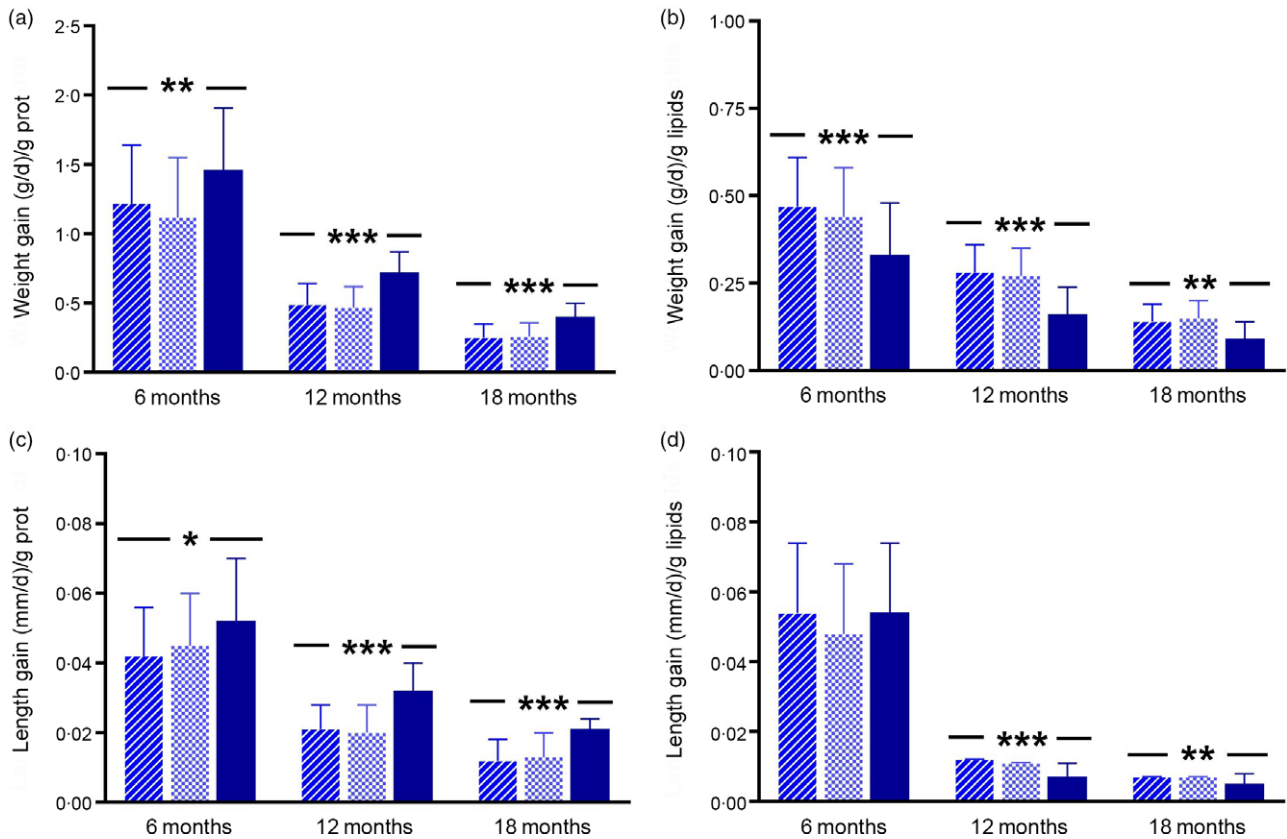
Fig. 3. Energetic efficiency analysis up to 18 months of age by feeding group. Data are marginal mean values and standard deviations. P-values were obtained by multivariate ANCOVA for group differences using multivariate general linear model, including the following confounders: maternal age, height and IQ. At 6 months of age, analysis was additionally adjusted by volume intake (ml/d) of infant formula or breast milk. For variables weight gain g/g protein; weight gain g/g lipids and length gain mm/g protein at 12 months of age, and length gain mm/g lipids at 6 and 12 months of age, P_{adj} corresponds to log-transformed for these variables. *P_{adj}-values < 0·05; ** P_{adj}-values < 0·01 and *** P_{adj}-values < 0·001. SF, standard infant formula; EF, experimental infant formula; BF, breastfed infants; IQ, intelligence quotient. ▨, SF; ▨, EF; ■, BF.

Energetic efficiency and length gain (mm/d). In a similar way, there were no significant differences up to 18 months of age in length gain/418·4 kJ (100 kcal) of milk and length gain/g of milk carbohydrates according to the feeding group (online Supplementary Table S4). However, at 6 months of age, length gain/g of milk protein was lower in the SF group compared with the BF infants ($P_{adj} = 0.023$); moreover, at 12 and 18 months of age, the formula fed groups showed lower length gain/g of milk protein than the BF group (12 months, $P_{adj} < 0.001$ and 18 months, $P_{adj} < 0.001$) (Fig. 3(c) and online Supplementary Table S4). Finally, we found that, at 12 months of age, length gain/g of milk lipids was higher in the infant formula groups compared with the BF group ($P_{adj} < 0.001$), while at 18 months of age it was higher in SF infants compared with the BF infants ($P_{adj} = 0.002$) (Fig. 3(d) and online Supplementary Table S4).

Discussion

The present study was aimed to perform an exhaustive analysis of growth patterns up to 18 months of life in COGNIS infants fed with a new bioactive compounds-enriched infant formula, compared with a standard infant formula and BF infants. Additionally, EE of infant formulas and breast milk was estimated. Our results suggest that the type of feeding during the first 6 months of life may determine infant growth patterns; length gain was higher and HC gain was lower in infants from the formula fed groups (SF or EF) compared with the BF infants. These significant differences were not found at 6–12 and 12–18 months. Moreover, the analysis of weight/length catch-up until 6 months of life suggested that EF and BF groups are characterised by higher proportion of normal catch-up growth compared with the SF group. Studies refer that HC may be associated with specific aspects of child development in healthy population[44,45]. Also, higher HC in infants at 4 and 6 months of age might be related to a better visual acuity at 12 months of life[41] and language development at 4 years old in those children fed with the enriched bioactive nutrients infant formula[46].

In general, growth is a result of a process depending on the availability of essential nutrients. A harmonious growth results from weight and length gains in appropriate proportion; an imbalance in weight gain might affect linear growth and could negatively impact on cognitive development at later ages[47]. Some studies suggest to analyse weight gain rates and linear growth as independent factors that could affect health and development in adulthood[48,49]. Therefore, infant weight gain is generally known as the primary indicator of healthy growth; higher weight gains between 3 and 12 months of age[50–52] have been related to higher risk of obesity and other metabolic disorders[53,54].

Growth patterns in infants during the first months of life are a topic of interest in paediatric research; growth characteristics have been described according to the type of feeding in early stages of life, given biological dynamics of human milk compared with infant formulas[6,55,56]. Results from the present study showed that the SF fed group was characterised by a lower proportion of infants with slow GV in length compared with the BF infants. In addition, when analysing the weight/age catch-up until 6 months of life, the formula fed groups (SF or EF) had significantly lower percentage of

slow growth infants compared with the BF group; conversely, the BF group had lower proportion of rapid WAZ catch-up. Moreover, the EF and BF groups are characterised by higher proportion of normal WLZ catch-up growth compared with the SF one. Research refers that infant formula intake is a risk factor for self-regulation satiety alteration[57], higher length gain[29], higher weight gain, rapid weight gain velocity, higher WAZ[58,59] and weight excess at later ages[60,61] compared with the BF infants. Since several years ago, infant formulas have been modified and enriched with bioactive nutrients trying to mimic those present in human milk to satisfy an optimal development and growth, providing the necessary amount of energy and nutrients[13,16]. Some studies have reported that infant formula intake implies an elevated protein intake, leading to increased secretion of insulin, insulin-like growth factor type 1 and adipogenic activity[62,63]; these mechanisms could be involved in growth patterns observed in formula fed infants; in this regard, infants fed with low protein content formulas show less risk for obesity during childhood[27]. Infant formulas tested in the present study follow the guidelines of the ESPGHAN Committee on Nutrition[64] and international and national recommendations for infant formula composition, and their protein content is within the minimum recommended range. Results from a study with a similar design to the present one indicated a rapid GV in formula fed infants compared with the breastfed ones, with no differences between standard formula or milk fat globule membrane supplemented formula[18].

The present study also evaluated whether differences in growth patterns between types of feeding with infant formula (SF or EF) or breast-feeding in the COGNIS study could be related to the EE of macronutrients present in infant formula and breast milk as a possible, and partial, explanation of the results obtained. To date, and despite that EE of infant formulas has been described, studies are largely based on short-term infant growth follow-up (until 6 months of life), and there is insufficient evidence to accurately compare EE in infant formula and breast milk[29,65]. The present study reports information about EE up to 18 months of age in formula fed and BF infants. Our data showed that BF infants had higher weight and length gain per g of milk protein compared with the formula fed infants up to 18 months of life, while milk lipids appear to be responsible for increased weight and length gain in those infants who received infant formula. These findings may be related to the nutritional composition of breast milk; in fact, breast milk provides high biological value proteins, optimal whey/casein ratio and adequate supply of amino acids[66–69]. Despite its higher content in lipids, breast milk also contains enzymes needed for digestibility and utilisation of fatty acids[70]. Both nutritional characteristics, together with its content in bioactive nutrients, hormonal and immune factors, could determine a better EE of breast milk compared with infant formulas in order to ensure an optimal infant growth and development. It is important to note that data from the present study cannot be attributed to a single specific component of infant formulas (enriched or not), but as a whole product designed to meet infant nutritional needs; moreover, there is likely a synergy among the different bioactive components, which could be associated with bioavailability and biological utilisation of nutrients. Currently, there is insufficient evidence to support the effect of DHA and

arachidonic acid enriched formula on growth and adiposity[30,71,72], or synbiotic supplementation on infants growth[23,30,73,74]. Effects on immune system and on microbiota structure and function have been described; these may be factors influencing children growth as well[23,73,74]. Thus, data obtained may be useful to develop further strategies not only focused on narrowing the nutritional gap but also the functional and metabolic gap, between infant formulas and human milk.

One of the strengths of the present study relies on long-term infant growth follow-up, as consequence of the longitudinal design of the COGNIS study, thus allowing a cross-sectional analyses of infant growth until 18 months of life, compared with other studies with shorter follow-up. Secondly, despite participants dropout at 18 months of life, statistical power was calculated to identify the validity of the results found in the present study. 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. Additionally, it is also important to highlight that 26 % of infants in the control group continued breast-feeding until 18 months, which allowed to estimate the EE and compare growth patterns between infants who received SF or EF (initiation and follow-on formulas), and those who were breastfed at long-term. Finally, COGNIS design also included data about socio-demographic and anthropometric characteristics both from parents and newborns, which were used as potential confounders in statistical models.

Research about infant growth has been largely focused on the analysis of growth in a transversal way (z-scores). Despite infant weight assessment is considered a global indicator of healthy child growth, our results suggest that it could be worth to analyse in depth how the weight GV and trajectory modify the length and HC, as well as the growth indicators (WAZ, LAZ, WLZ and HCZ) during childhood. Current results have an added value due to the methodology used, based on different techniques with z-scores trajectories, GV using the WHO growth standards and classification according to growth rate (catch-up) between follow-up visits. Thus, this methodology could provide a basis to evaluate long-term potential impact of type of feeding at early age on infant GV and trajectory. Moreover, it can be useful to provide detailed and individualised guidelines for the introduction of complementary feeding, according to nutritional needs and infant growth patterns (especially for those who present rapid or slow growth trajectories), ensuring an adequate and normal growth for age.

However, there are limitations that must be acknowledged. First, due to ethical reasons, breast milk must be offered on demand with no limits in its volume or duration. Consequently, volumes of breast milk intake were obtained from 3-d dietary records as well as theoretical estimates based on previously published findings[39,40]. For future studies, we suggest to weight the infant before and after being breastfed to know more accurately breast milk volume intake. Second, breast milk is a nutrient with a varying nutritional composition, both in a time-day basis and over time, to adapt to infants nutritional needs. Our study has not an individual analysis of the breast milk of each infant during the follow-up; therefore, composition in the present study was estimated based on a full mature breast milk composition as reported in the USDA National Nutrient Database for Standard Reference[66]. It would be interesting in later studies to analyse the composition of breast milk individually and describe the composition of nutrients during the first 2 years of age. Third, our goal was to estimate EE of infant formulas (SF or EF) and breast milk, and we did not include complementary feeding in the analysis performed; thus, it would be interesting to analyse the complementary feeding in the three COGNIS groups in future studies. Finally, as previously reported[41], COGNIS study design implies the non-randomisation of the BF group, in contrast to both SF and EF groups, which could explain differences in maternal age, height and IQ baseline characteristics.

In summary, herewith we suggest that type of feeding received between birth and the first 6 months of life could be responsible for differences in infant GV and catch-up growth. GV during first 6 months, which may be influenced by feeding, seems to be the main predictor of subsequent growth patterns. Moreover, in infants fed with the enriched bioactive nutrients formula, higher HC at 6 months of age was found in the present study, which could be related to better visual acuity[41] and language development at 4 years old[46], as previously reported. EE of breast milk nutrients seems to be responsible for its benefits on infant growth. Our results suggest that traditional methodology used for growth analysis may be insufficient to characterise the growth trajectory during childhood. In fact, traditional methodology is based on the parameters and indicators in a cross-sectional way, but not on an evolutionary one. However, analysis of weight, length and HC gains as a function of time and velocity, and how the GV changes, may better define the growth pattern at later stages. Further research based on long-term growth monitoring is necessary to establish the effects of early nutrition (infant formula fed or breast milk and complementary feeding) on body composition as an indicator of metabolic long-term health risks, and children's growth later in life.

Supplementary material

For supplementary materials referred to in this article, please visit https://doi.org/10.1017/S000711452100057X

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