Current Nutrition Reports (2022) 11:283–300
https://doi.org/10.1007/s13668-022-00410-7

MATERNAL AND CHILDHOOD NUTRITION (AC WOOD, SECTION EDITOR)

Supplementation of Infant Formula and Neurodevelopmental Outcomes: a Systematic Review

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Accepted: 7 March 2022 / Published online: 25 March 2022

Abstract

Purpose of the Review The aim is to examine data from clinical trials and prospective longitudinal studies that evaluate the effect of infant formula supplements on the cognitive function of children.

Recent Findings A total of 300 articles from 2000 to 2021 were selected. The most researched IF supplements were initially long-chain polyunsaturated fatty acids (LC-PUFA), some proteins and, recently, milk fat globule membrane (MFGM). Supplementation of IF with LC-PUFA led to some positive effects on specific cognitive functions or no effect; however, there was no consistent benefit for cognitive function. Modifying the amount of proteins did not affect the children's neuropsychological tests. Supplementation of IF with MFGM and its components had beneficial effects on child cognitive development in the short term, but no effect was observed in the long term.

Summary Further studies are needed to confirm the safety of supplementation on the development of cognitive function in children fed with infant formula.

Keywords Infant formula · Infant neurodevelopment · Infant nutrition · Nutritional supplementation

Introduction

Research into nutrition provides an increasing amount of evidence on its importance in childhood and long-term effects in the growth and development of the child, specifically for the development of the central nervous system, which begins in the prenatal stage and continues until the first years of life.

This article is part of the Topical Collection on *Maternal and Childhood Nutrition*

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The preferred diet for a baby during its first months is breast milk. However, for many children, infant formula (IF) is the alternative feeding option. In Spain, the prevalence of breastfeeding at hospital discharge is 85.3%. This frequency drops to 53.4% at 3 months, 46.1% at 4 months and 7.2% at 6 months [1]. These values are similar to those of other developed countries. Thus, a significant percentage of children in our environment begin or are incorporated into artificial breastfeeding in this critical period of the infant's physical and neurobehavioural development.

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The first objective of the research and industry has been to approximate the nutritional composition of infant formulas to breast milk, which is considered the reference standard. This approach has since been expanded with the aim to also transfer the functional benefits of breast milk to IFs, such as the effect on the child's neurodevelopment. The first 2 or 3 years of life are essential for the correct structural and functional development (neuronal proliferation, myelination and synapse formation) of the nervous system [2].

In order to promote neurodevelopment, the food industry, endorsed by various studies and according to the regulations of the Food Safety Agencies, which regulate the safety and efficacy of IF components, has continued to modify IFs to achieve the best effects on child growth and development. The components initially most researched were long-chain polyunsaturated fatty acids (LC-PUFA), protein supplements, prebiotics and probiotics and more recently the membrane of milk fat globules (MFGM) [3].

Interest in LC-PUFA, such as docosahexaenoic acid (DHA) and arachidonic acid (ARA), began when it was found that these fatty acids are the most abundant in the structure of nervous tissue and continue to accumulate in the baby's nervous system during early infancy. Breast milk contains higher amounts of LC-PUFA than cow's milk [4, 5]. However, although there have been many studies on LC-PUFA, its effect on the children's medium- and long-term cognitive function was found to be unclear in various systematic reviews dating from the early 2000s [6–8] until 2020 [9••].

Other studies have focused on evaluating the effect of prebiotics and probiotics incorporated in infant milk on the baby's gut microbiome and neurocognitive development in the early stages of life. Intestinal microbiota seems to play an important role in child's development at immune, endocrine and neurological level, although studies analysing the human microbiome–gut–brain axis are still few [10].

Similarly, in recent years, MFGM has aroused a growing interest in the scientific community due to its biological activities that are potentially beneficial for human health. MFGM is composed of a triglyceride-rich nucleus surrounded by a three-layered membrane and comprises a monolayer of polar lipids and a lipid bilayer. MFGM consists of phospholipids such as sphingomyelins, phosphatidylcholines, gangliosides and different proteins, including lactoferrin and mucins [11•]. Some recent studies have described beneficial effects on neural development and defence against infections in infants [11•, 12, 13]. Infant formulas traditionally have not included the MFGM fraction, but dairy technology has now made adding bovine MFGM technically feasible.

To our knowledge, no systematic review has comprehensively examined the effect of the different nutritional components of IF on child neurodevelopment. Therefore, we propose carrying out a systematic review of the effect of the different components incorporated into infant formula on the cognitive development evaluated at different ages of healthy term children.

Methods

Search Strategy

The PubMed electronic literature database was searched until September 20, 2021. The search strategy included terms related to the exposure and outcome of interest, as follows: ((“infant formula” [Mesh] OR “supplemented milk”) AND (neurodevelopment* OR “neurodevelopmental disorders” [Mesh] OR verbal OR language OR cognition OR cognitive) AND infant). We used PubMed functions such as truncation and MeSH heading. In addition, the reference lists of related literature reviews were searched by hand.

Selection Criteria

We selected studies that were randomized controlled trials (RCTs) and observational studies assessing the effect of supplemented infant formulas on different aspects of the babies' neurodevelopment. The study population of the research included in the review was healthy term infants fed with infant formulas. Studies carried out with preterm infants, small-for-gestational-age babies or with other disorders, as well as those that assessed other birth outcomes, physical development or growth were excluded.

Data Extraction and Quality Assessment

The information from the studies, extracted and summarized by two researchers independently, included the country, type of study, sample, type of supplementation, duration and different groups of comparison, cognitive outcomes assessed and psychological tests used. The data are not comparable between different types of supplementation, and therefore, the results are discussed in separate sections accordingly.

We used the revised CONSORT checklist [14] and the STROBE checklist [15] to assess the quality of RCTs and observational studies, respectively. The key elements that are critical for good study design in the current analysis were operationalized and a numerical score was assigned to determine how well the included articles met it. For the CONSORT checklist, items number 5 (interventions), 9 (allocation concealment method), 11a (blinding) and 12a (statistical methods) received 0, 1 or 2 points depending on the degree of compliance. Item number 7a (sample size) received 1 point if the authors indicated how sample size was calculated and 0 points otherwise. Therefore, the quality score for RCT would range from 0 to 9 points. Articles were rated as "low quality" if they scored 0 to 5 points, "moderate quality" if they scored 6 to 7 points, and "high quality" if they scored 8 to 9 points. The same was done for the STROBE checklist: items number 5 (setting), 6a (eligible criteria) and 9 (bias) received 0, 1 or 2 points, while item number 10 (sample size) received 0 or 1 points. In this case, the quality score for observational studies would range from 0 to 7 points. Articles were rated as "low quality" if they scored 0 to 3 points, "moderate quality" if they scored 4 to 5 points and "high quality" if they scored 6 to 7 points. The quality of the present systematic review was also assessed using the PRISMA guide [16].

Results

We identified a total of 295 articles from the search in the PubMed electronic databases. Based on title and abstract, 61 were eligible for full-text reading, out of which met the inclusion criteria. In addition, five more studies were identified by hand searching the review reference lists. Finally, 25 studies (22 RCTs, seven prospective cohorts and one cross-sectional study) were included in the present systematic review. The most common reasons for excluding records during the selection process were that the article was a systematic review or meta-analysis, a study that did not report the population or outcome of interest, or an animal study (Fig. 1).

Characteristics of Included Studies

The studies reviewed were published between 2000 and 2021 and varied widely in size, location and type of infant formula supplementation; however, they all focused on child neurodevelopment. The characteristics of the studies are shown in Table 1. In terms of location, 11 studies were conducted in the United States (US), three in The Netherlands, four in Spain, two in Sweden, two in the United Kingdom (UK), one in China and one in Indonesia. Two other studies were multicentred studies including subjects from different European countries.

Based on the scores in the CONSORT and STROBE checklists, 12 studies had a "high" quality and 12 were rated "moderate".

Infant Formula Supplementation

Half of the studies, especially the older ones, focused on LC-PUFA, and mainly on docosahexaenoic acid (DHA) and arachidonic acid (ARA). However, one study researched infant formulas supplemented with different amounts of proteins. More recent studies assessed the effect of new ingredients, such as triglyceride sn-2 palmitate, gangliosides from complex milk lipid and bovine MFGM.

In terms of the time and duration of using the supplemented infant formulas, seven studies researched the first 2–3 postnatal months, five studies researched the first 4 or 6 post-natal months, nine studies researched up to 12 months and three studies researched up to 18 months.

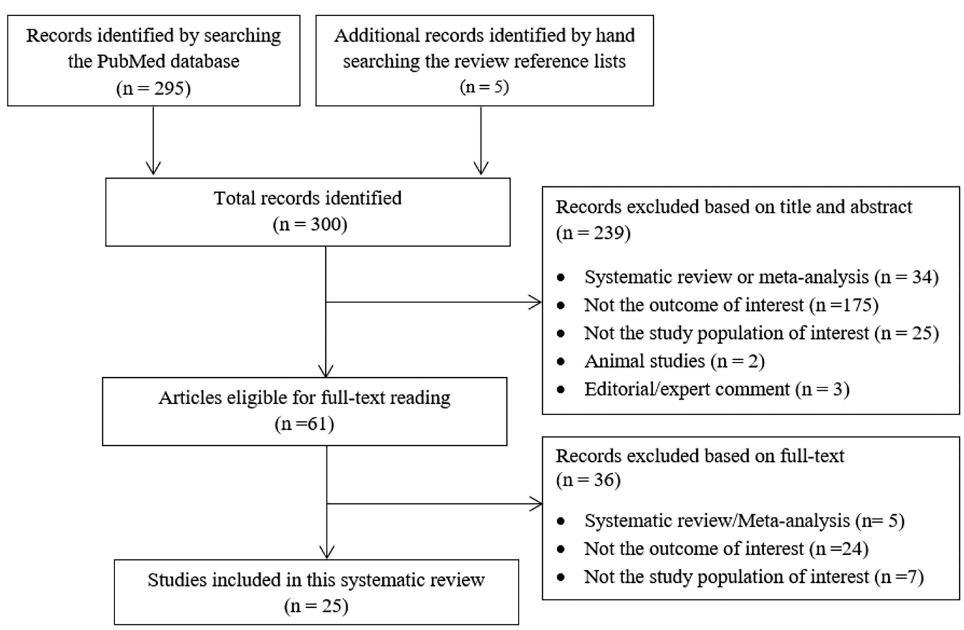

Fig. 1 Flow diagram of selected studies

Table 1 Characteristics of the studies included in the revision

Reference/country	Study design	Sample/groups	Supplementation duration	Outcome (age)	Assessment tool	Confounders	Results	Effect	Quality
Birch et al. [17], US	RCT	56 infants: 1. Control -IF ($n = 20$) 2. DHA 0.35% -IF ($n = 17$) 3. DHA 0.36% + ARA 0.72% -IF ($n = 19$)	First 17 weeks	Cognitive function (18 months)	BSID-II	None	DHA + ARA group presented higher scores on the MDI compared to control Both IDM and IDP showed a significant developmental for LC-PUFA groups Diet groups did not differ for the language subscale, PDI or behaviour	Positive	Moderate
Auestad et al. [18], US	RCT	276 infants: 1. Control -IF ($n = 65$) 2. DHA 0.20% -IF ($n = 65$) 3. DHA 0.12% + ARA 0.43% -IF ($n = 66$) 4. Breastfed ($n = 80$)	First 12 months	Neurodevelopment (3.2 years)	Stanford-Binet, PPVT-III	Maternal: age and education Infant: birth size, weight, sex and age	No difference in neurodevelopment between any diet groups	Not observed	Moderate
Bouwstra et al. [19], The Netherlands	RCT	474 infants: 1. Control -IF ($n = 169$) 2. DHA 0.30% + ARA 0.45% -IF ($n = 146$) 4. Breastfed ($n = 159$)	First 2 months	Neurodevelopment (18 months)	Hempel Scales, BSID-II	Maternal: parity and HOME score Parental: education Infant: size and age	Bayley MDI and PDI scores did not differ between the three groups	Not observed	High
Birch et al. [20], US	RCT	84 infants: 1. Control -IF ($n = 19$) 2. DHA 0.35% -IF ($n = 16$) 3. DHA 0.36% + ARA 0.72% -IF ($n = 17$) 4. Breastfed ($n = 32$)	First 17 wks	Cognitive function (4 years)	WPPSI-R	None	LC-PUFA and breastfed groups had better IQ scores than the control, although not statistically significant	Not observed	Moderate
Jing et al. [21], US	Longitudinal study	41 infants: 1. DHA + ARA -IF ($n = 20$) 2. Breastfed ($n = 21$)	First 2–3 months	Behaviour (3 and 6 months)	BSID-II	None	There was no between-group difference for behaviour at age 3 and 6 months	Not observed	Moderate

Table 1 (continued)

Reference/country	Study design	Sample/groups	Supplementation duration	Outcome (age)	Assessment tool	Confounders	Results	Effect	Quality
Drover et al. [22], US	RCT	229 infants: 1. Control -IF ($n = 114$) 2. DHA 0.36% + ARA 0.72% -IF ($n = 115$)	Depending on RCT: first 12 months Since first 1.5 to 12 months Since 4–6 to 12 months	Cognitive function (9 months)	MEA	Parental: education	LC-PUFA groups had higher cognitive scores than the controls	Positive	High
de Jong et al. [23], The Netherlands	RCT	474 infants; 1. Control -IF ($n = 169$) 2. DHA 0.30% + ARA 0.45% -IF ($n = 146$) 3. Breastfed ($n = 159$)	First 2 months	Neurological condition (9 years)	TECMND	Maternal: education, smoking, delivery type, obstetrical optimality score, hypertension, infant: sex, birth weight and birth Apgar	Neurological optimality and severity and type of MND did not differ between the two formula groups Breastfed group showed significantly less fine manipulative dysfunction than formula groups	Not observed	Moderate
Gale et al. [24], UK	Longitudinal study	241 infants: 1. Control -IF ($n = 46$) 2. DHA -IF ($n = 65$) 3. Breastfed ($n = 130$)	First 6 mo	Neuropsychological function (4 y)	WPPSI-R, NEPSY	Maternal: education, social class, IQ, receipt of means-tested benefits Infant: age at birth and birth weight	DHA group had total IQ score higher than the control group Cognitive and neuropsychological tests were not different between the breastfed and control groups	Positive	High
Colombo et al. [25], US	RCT	122 infants: 1. Control -IF ($n = 31$) 2. DHA 0.32% + ARA 0.64% -IF ($n = 32$) 3. DHA 0.64% + ARA 0.64% -IF ($n = 26$) 4. DHA 0.96% + ARA 0.64% -IF ($n = 33$)	First 12 months	Cognitive function (4, 6 and 9 months)	EEG	None	All DHA + ARA groups had lower heart rates than the control; there was no dose response for this effect	Negative	Moderate

Table 1 (continued)

Reference/country	Study design	Sample/groups	Supplementation duration	Outcome (age)	Assessment tool	Confounders	Results	Effect	Quality
Drover et al. [26], US	RCT	117 infants: 1. Control -IF ($n=28$) 2. DHA 0.32% + ARA 0.64% -IF ($n=29$) 3. DHA 0.64% + ARA 0.64% -IF ($n=32$) 4. DHA 0.96% + ARA 0.64% -IF ($n=28$)	First 12 months	Cognitive function (18 months)	BSID-II	None	There were no differences between groups in MDI, PDI or behaviour scores	Not observed	Moderate
Keim et al. [27], US	Longitudinal study	358 infants: 1. DHA + ARA -IF ($n=65$) ($n=39$) 2. Breastfed ($n=207$) 3. Partially breastfed ($n=112$)	First 4 months	Cognitive development (12 months)	MSEL	Maternal: education, race ethnicity and smoking Infant: sex and preterm status	There were no differences between groups in visual reception, language or motor skills, or overall cognitive development LC-PUFA content in breast milk or formula was not associated with cognitive development	Not observed	Moderate
Drover et al. [28], US	RCT	131 infants: 1. Control -IF ($n=30$) 2. DHA 0.32% + ARA 0.64% -IF ($n=33$) 3. DHA 0.64% + ARA 0.64% -IF ($n=34$) 4. DHA 0.96% + ARA 0.64% -IF ($n=34$)	First 12 mon	Language development (2, 3.5 years)	PPVT-III, BBCS-R	Maternal: education Infant: sex	There were no differences between groups in the BBCS-R score In the PPVT-III, the control group had a higher score than both the DHA 0.32% and DHA 0.96% groups at age 2 years, but not at 3.5 years	Not observed or negative	High

Table 1 (continued)

de Jong et al. [29], The Netherlands	RCT	341 infants: 1. Control -IF ($n = 123$) 2. DHA 0.30% + ARA 0.45% -IF ($n = 91$) 3. Breastfed ($n = 127$)	First 2 month	Cognition and behaviour (9 years)	WASI, NEPSY, EAMS, CBCL	Maternal: education, IQ, pre-pregnancy BMI, smoking Infant: sex	No beneficial effect of LC-PUFA on cognitive development was found Breastfeeding was associated with better performance in IQ tests	Not observed or negative	Moderate
Gurnida et al. [30•], Indonesia	RCT (pilot study)	91 infants: 1. Control -IF ($n = 30$) 2. Ganglioside -IF ($n = 29$) 3. Breastfed ($n = 32$)	From 2 to 8 weeks until 6 months	Cognitive function (6 months)	GMDS	Maternal: education, occupation, family size Infant: age, haemoglobin, ferritin and total iron-binding capacity	Ganglioside-group scored higher for GMDS tests than the control Cognitive development scores for the ganglioside-group did not differ from the breastfed group	Positive	Moderate
Willatts et al. [31], UK, Belgium and Italy	RCT	235 infants: 1. Control -IF ($n = 76$) 2. DHA 0.30% + ARA 0.45% -IF ($n = 71$) 3. Breastfed ($n = 88$)	First 4 months	Cognitive function (6 years)	WPPSI-R, DNT, MFF	Maternal: age and education Infant: birth weight, head circumference and age at test	There were no differences between ARA + DHA and control groups for the full-scale IQ, attention or MFFT error The LC-PUFA group was significantly faster at processing information	Not observed or positive	High

Table 1 (continued)

Colombo et al. [32], US	RCT	81 infants: 1. Control -IF ($n=18$) 2. DHA 0.32% + ARA 0.64% -IF ($n=21$) 3. DHA 0.64% + ARA 0.64% -IF ($n=18$) 4. DHA 0.96% + ARA 0.64% -IF ($n=24$)	First 12 months	Cognitive function (18 months–6 years)	BSID-II, BCDI, DR, Bear-Dragon, Go/No Go, Stroop, DCCS, PPVT-III, WPPSI-R	Maternal: PPVT-III and household income	LC-PUFA did not influence language development (BSID-II) or performance (MBCDI) at 18 months. However, positive effects were observed from 3 to 5 years on rule learning and inhibition tasks, the PPVT-III test at 5 years and the WPPSI-III at 6 years of age Effects of LC-PUFAs were not found on other cognitive scales	Not observed or positive	High
Timby et al. [33], Sweden	RCT	240 infants: 1. Control -IF ($n=80$) 2. Low-energy, low-protein MFGM -IF ($n=80$) 3. Breastfed ($n=80$)	First 6 months	Neurodevelopment (12 months)	BSID-III	Maternal and paternal: age, education and smoking	The MFGM-group obtained better cognitive test scores at 12 months than the control No significant differences in the motor or verbal domains were found between formula groups	Not observed or positive	High

Table 1 (continued)

Liao et al. [34••], US	RCT	69 infants: 1. Control -IF ($n=28$) 2. DHA 0.32% + ARA 0.64% -IF ($n=21$) 3. DHA 0.64% + ARA 0.64% -IF ($n=18$) 4. DHA 0.96% + ARA 0.64% -IF ($n=24$)	First 12 mo	Behaviour and event-related potentials (ERPs) (5.5 years)	Bear-Dragon Go/No Go, EEG	None	Behaviour scores did not differ between formula groups The control group had lower ERP P2 amplitude than the LC-PUFA-group There was a significant difference in ERP N2 between the LC-PUFA groups	Not observed or positive	Moderate
Escribano et al. [35], Germany, Belgium, Italy, Poland and Spain	RCT	538 infants: 1. Low protein -IF ($n=184$) 2. High protein -IF ($n=170$) 3. Breastfed (control -IF, $n=184$)	First 12 months	Neurodevelopment (8 y)	ROT, RAVLT, CPT, HVOT, Animals–FAS, NEPSY, Symbol digit modalities test, Grooved Pegboard, Stroop, Kaufman-ABCII Pattern reasoning, Children's Color Trail Test	Maternal: marital status, education, nationality, smoking during pregnancy and delivery type Infant: gestational age, sex, head circumference at birth and at age 8 years	There were no significant differences between feeding groups in any of the neuropsychological domains or behaviours	Not observed	High

Table 1 (continued)

Nieto-Ruiz et al. [36], Spain	RCT	168 infants: 1. Control -IF ($n=62$) 2. MFGM + LC-PUFAs -IF ($n=69$) 3. Breastfed ($n=37$)	First 18 months	Neurodevelopment (2, 3 and 4 months)	General movements test	None	Neurological development was good in all infants at age 4 months, and no statistically significant differences were found between feeding groups at any point in time	Not observed	High
Li et al. [37], China	RCT	451 infants: 1. Control -IF ($n=228$) 2. MFGM -IF ($n=223$)	First 12 months	Neurodevelopment (12 and 18 months)	BSID-III and MBCDI	Maternal: age, education, number of family members, family income, vitamin or DHA supplement, smoking Infant: sex and birth weight	The MFGM-group scored higher than the control for the cognitive, language and motor domains at age 12 months No differences were observed in any Bayley-III domain at age 18 months, but scores of some subcategories of the MBCDI were higher in the MFGM-group than in the control	Positive	Moderate

Table 1 (continued)

Nieto-Ruiz et al. [39], Spain	RCT	70 infants: 1. Control -IF ($n = 29$) 2. MFGM + LC-PUFAs -IF ($n = 41$) 3. Breastfed ($n = 33$)	First 18 months	Behavioural and psycho-emotional disorders (18 and 30 months)	CBCL	Maternal: education, socioeconomic status and place of residence	No differences were found in CBCL scores between feeding groups at age 18 months At 2.5 years old, the MFGM + LC-PUFAs group had had lower scores in affective problems than the control group The MFGM + LC-PUFAs and breastfed groups showed lower scores in externalizing problems than the control at 30 months of age	Positive	High
Nieto-Ruiz et al. [39], Spain	RCT	122 infants: 1. Control -IF ($n = 46$) 2. MFGM + LC-PUFAs -IF ($n = 43$) 3. Breastfed ($n = 33$)	First 18 months	Language development (4 years)	PLON-R	Maternal: age, education, IQ and socioeconomic status Paternal: age and education Infant: sex	The MFGM + LC-PUFAs group scored higher in language use and spontaneous oral expression than the control The control group showed worse scores in the PLON-R total score than the breastfed group	Positive	High

Table 1 (continued)

Timby et al. [40], Sweden	RCT	178 infants: 1. Control -IF ($n = 56$) 2. Low-energy, low-protein MFGM -IF ($n = 58$) 3. Breastfed ($n = 64$)	First 6 months	Neurodevelopment (6.5 years)	WISC-III, Brown-ADD, QbTech, CBCL, TRF	Infant: gestational age	There was no difference in any of the parameters tested in any of the diet groups	Not observed	High
Wu et al. [41], China	RTC	199 infants: 1. Control -IF ($n = 67$) 2. sn-2 palmitate -IF ($n = 66$) 3. Breastfed ($n = 66$)	First 24 weeks	Neurodevelopment (16 and 24 weeks)	ASQ-3	Maternal: education	sn-2 palmitate group scored higher than control for fine motor skills The beneficial effects of the sn-2 palmitate group on infant neurodevelopment was associated with the increased gut Bifidobacteria level	Positive	Moderate

US United States, *UK* United Kingdom, *RCT* randomized clinical trial, *IF* infant formula, *LC-PUFA* long-chain polyunsaturated fatty acids, *DHA* docosahexaenoic acid, *ARA* arachidonic acid, *MFGM* milk fat globule membrane, *BSID-II* Bayley Scales of Infant Development, 2n edition, *PPVT* Peabody Picture Vocabulary Test, *WPPSI-R* Wechsler Preschool and Primary Scale of Intelligence-Revised, *EEG* electroencephalographic, *MEA* Mean-End Analysis, *TECMND* Touwen's Examination of the Child with Minor Neurological Dysfunction, *NEPSY* Developmental NEuroPSYchological Assessment, *MSEL* Mullen Scales of Early Learning, *BBCS-R* Bracken Basic Concept Scale-Revised, *WASI* Wechsler Abbreviated Scale of Intelligence, *EAMS* Everyday Attention and Memory Scale, *CBCL* Child Behavior Checklist, *GMDS* Griffiths Mental Development Scale, *DNT* Day-Night Test, *MFFT* Matching Familiar Figures Test, *MBCDI* MacArthur-Bates Communicative Development Inventory, *DR* Delayed Response, *DCCS* Dimensional Change Card Sort, *ROT* Recall of Objects Test, *RAVLT* Rey Auditory Verbal Learning Test, *CPT* Continuous Performance Test, *HVOT* Hooper Visual Organisation Test, *MBCDI* The MacArthur-Bates Communicative Development Inventories, *PLON-R* Oral Language Task of Navarra-Revised, Brown-ADD, Brown Attention-Deficit Disorder Scales for Children and Adolescents, *QbTech* Quantified Behavior test, *TRF* Teacher Report Form, *MDI* Mental Development Index, *PDI* Psychomotor Development Index, *BRS* Behavior Rating Scale, *PSL* Preschool Language Scale

Child's Cognitive Assessment

The cognitive evaluation of the child was carried out at different ages between 2 months and 9 years old, depending on the study, and in some cases, the authors repeated the evaluation at successive ages. Thus, 11 studies performed the cognitive assessment in children younger than 12 months, four studies at 12 months of age, six studies when children were aged 18 months, six more at ages of 2–4 years, four studies in 5- to 6.5-year-old children and three in children of 8 to 9 years of age.

The test used for assessing the child's cognitive development depends largely on the child's age. Thus, the second and third editions of the Bayley Scale of Infant Development (BSID) were only used for children under 18 months of age. The BSID includes different aspects of neurodevelopment, including mental, motor and language development. The MacArthur-Bates Communicative Development Inventory (MBCDI), the Ages and Stages Questionnaire (ASQ-3), the Mullen Scales of Early Learning scores, the Hempel Scales, the General movements (GM's) test, the Griffiths Mental Development Scale (GMDS) and the two-step means-end problem-solving task were other tests used in very young children to evaluate many different areas of cognitive function. From 2 years of age onwards, the Wechsler Preschool and Primary Scale of Intelligence-Revised (WPPSI-R), the Peabody Picture Vocabulary Test (PPVT-III), the Developmental Neuropsychological Assessment (NEPSY), Mullen Scales of Early Learning and the Child Behavior Checklist (CBCL) were the most commonly used tests to assess IQ and neuropsychological functions.

In addition, three studies assessed the effect on behavioural and socio-emotional development through the Child Behavior Checklist (CBCL 18 months–5 years and CBCL 6–18 years) answered by parents. Other five studies measured the electroencephalographic (EEG) activity to check physiological brain development. Four of them are in children at 6 months of age or younger and the other study with 5.5-year-old children.

Discussion

The composition of infant milk has been continually improved to make it as similar as possible to breast milk, so that formula milk offers the same physiological effects as breastfeeding. Therefore, this review examined the effect of the different nutritional components incorporated into IF, including the most recent compounds, on different assessments of child neurodevelopment.

Long-Chain Polyunsaturated Fatty Acids

It is known that the cognitive capacity of breastfed children is superior to that of children fed IF and that there is a high accumulation of DHA and ARA in the brain [42]. IF-fed infants are also known to have lower levels of LC-PUFA in the cerebral cortex than breastfed infants [43], suggesting that the standard IF content may not be effective in meeting all the fatty acid requirements of the infant. This occurred when standard IF contained only the precursor fatty acids of PUFA, that is, linoleic acid (precursor of ARA) and alpha-linolenic acid (precursor of DHA). All of this has generated substantial interest in determining the effects of these LC-PUFA on the growth and development of the child's brain [9••, 44•].

The first evidence that DHA improves cognitive function comes from studies conducted in 1992 in very low-birth-weight premature infants [45]. Subsequently, several clinical trials compared IFs supplemented with DHA and ARA with IF without supplementation [17, 21, 22, 25, 26, 28, 32] and, on other occasions, also compared to breastfed children [18–20, 23, 24, 27, 29, 31]. The data from these studies, while showing some benefits for a specific function or no effect, did not demonstrate a clear or consistent benefit of supplementing IF with LC-PUFA for full-term infants in the later child cognitive function assessments. These observations are consistent with the findings of the first systematic reviews from the 2000s [6–8], and with others published later in 2016 [44•] and 2017 [46]. Only a few studies adjusted the results for several potentially confounding variables [18, 19, 23, 24, 29, 31, 32].

Many of these studies researched the effect of different doses of LC-PUFA, mainly DHA, because as it is more dependent on intake, its value in breast milk was quite variable in lactating mothers and at the population level. In contrast, the ARA in breast milk does not depend on intake. This has made it difficult to determine the most optimal amount of DHA for supplementing the IF. However, although the optimal balance is not yet known, it has been suggested that the amount of DHA in infant formula should not exceed the amount of ARA [44•].

Recently, Verfuerden et al. [9••], in addition to a systematic review, carried out a meta-analysis to evaluate the effect of IF supplemented with LC-PUFA on the cognitive function evaluated in children within a wide age range (2, 5–16 years), compared to IF with no supplementation. Clinical trials conducted with term infants from Europe and the United States were included. The cognitive assessment was estimated for children between 3.3 and 16 years of age. The first meta-analysis included studies that assessed cognitive outcome in children aged 4–6 years, using the WPPIr. The data come from the Study of the six European countries [31, 47–51], from the

DIAMOND study from the USA (Dalas and Kansas) [25, 26, 28, 32, 34••, 52–54], and two unpublished clinical trials from England. These studies did not observe any difference between the supplemented and un-supplemented group (mean difference − 0.04 points, 95% CI − 5.94 to 5.85). They also conducted a meta-analysis including studies with children evaluated in a broader age range (4–16 years old) and using different cognitive assessment tests. We included articles that used the WPPIr, the PPVT at 3.5 years [18,28,32,], WPPSI [20, 31, 32], Stanford-Binet at age 3.3 years [18, 55] and WASI in children of 9 and 16 years of age [23, 29]. The observed mean difference was not significant: − 0.10 (95% CI − 0.32 to 0.12). The results of these meta-analyses agreed with the previously observed lack of effect of LC-PUFA supplementation on long-term cognitive development in full-term infants. Similar negative results were obtained in a meta-analysis carried out in premature infants. Other prospective longitudinal studies [21, 24, 27] or clinical trials [22] not included in the previous meta-analysis obtained similar results.

In addition to the use of these cognitive assessment tests, the response to supplementation with DHA and ARA has also been assessed by brain electrophysiology. In the DIAMOND cohort, the study measured the evoked response potentials in 5.5-year-old children and observed that the group supplemented with DHA and ARA during infancy showed better responses than the non-supplemented group, indicating a more mature inhibitory control. The children were later evaluated at 9 years of age through structural, functional and metabolic studies of the brain (magnetic resonance imaging, magnetic resonance spectroscopy and magnetoencephalography), and a more mature brain performance was observed in the supplemented compared to the non-supplemented group [34••].

Considering this lack of evidence, some authors have suggested that early measures of cognitive function in studies, such as the Bayley Scales of Child Development, may not be able to detect differences in cognition in young children [9••, 44•, 56]. Likewise, the existence of genetic polymorphisms (1 FADS2), which modulate the ability to synthesize ARA and DHA, can modify the effect of the supplementation study, which has not been considered in these clinical trials [57]. Other authors have hypothesized that there are undiscovered links between LC-PUFA and other fats, such as cholesterol, or other nutrients or substances that influence brain development [44•]. It has also been suggested that the potential harms of LC-PUFA may be related to their food source, so that PUFAs from eggs, fish, algae and fungi may not have the same functional effects as PUFAs from breast milk. Furthermore, the DHA content of breast milk is variable and is highly influenced by the mother's diet, which makes it difficult to clearly determine its optimal dose [58]. This uncertainty was reflected in the range of administered LC-PUFA doses in clinical trials. Only a few studies in our review adjusted the results for several potentially confounding variables [18, 19, 23, 24, 29, 31, 32]. A possible bias in conducting meta-analyses is the lack of studies with negative results because these studies are not published, as well as the very limited number of studies that assessed specific cognitive tasks [9••, 44•]. Also, within the factors that may intervene in the lack of positive results can be found that there is no control of many other variables that may intervene in neurodevelopment in the short and long term: child-maternal figure link, genetic load (by IC), subsequent infant feeding or level of stimulation, among others.

In the decision to supplement IF with LC-PUFA, it is important to consider the absence of adverse effects on the growth and development of children. However, although not often, some negative effects have been described, such as lower vocabulary scores at 14 months of age [55], or some damage in other domains, such as an increased risk of bronchopulmonary dysplasia in preterm infants [59].

Therefore, given the lack of evidence of the benefits of supplementing infant formula with LC-PUFA for cognitive function in full-term infants, it seems sensible to be prudent in endorsing the widespread supplementation, even more so if we consider the lack of evidence on other functional results, or on the exclusion of possible future damages, in addition to considering the additional costs generated by supplementation.

Proteins

Few studies have researched the effect of protein on neurodevelopment. Escribano et al. [35] conducted a randomized clinical trial with children from five European countries fed with a higher or lower protein content formula during the first year of life. Children were assessed at the age of 8 years with a neuropsychological set of tests. None of these studies found an improvement effect on the child's neurodevelopment, either in the short (12 months) [33] or long term (6–8 years) [35, 40].

Probiotics, Prebiotics and Symbiotics

The intestinal microbiota can be modulated by the intake of probiotics, prebiotics or a combination of both, symbiotics. Gut microbiota has been related to the development of neural networks and neurotransmitter response, so a correct state of the gut microbiome in infants may be a key to good neurodevelopment [60, 61].

In this review, we did not find any studies that exclusively relate probiotic or prebiotic supplementation in infant formulas to neurodevelopmental improvement; however, it has been confirmed that these components improve the intestinal microbiome and are related to correct brain development.

Milk Fat Globule Membrane

An important component that is currently gaining attention is milk fat globule (MFG). Increasing evidence suggests that the structure of MFG and the bioactive components of MFGM could benefit the paediatric population by assisting in the structural and functional maturation of the brain [11•].

Infant formulas have traditionally not included the bovine MFGM fraction. This explains one of the differences between the composition of IFs and that of breast milk. However, in recent years, dairy technology has made it possible to add bovine MFGM [62] to create formulas that mimic breast milk and thus provide the infant with the possible benefits. Different studies have analysed the benefits of adding MFGM to infant formulas for cognitive development. Specifically, two double-blind, randomized controlled clinical trials show that supplementation of infant formulas with MFGM has promising effects on neurodevelopment. In both studies, a sample of breastfed infants was used as the reference group. Gurnida et al. [30•] evaluated the impact on cognitive function of fortifying infant formula with gangliosides from bovine milk in 30 infants using the Griffiths Mental Development Scale at 6 months. After adjusting for socioeconomic variables, they observed that the Hand–Eye Coordination, Executive IQ and General IQ tests were better, and the study group had higher levels of gangliosides in the blood than the control group with non-enriched formula. Subsequently, Timby et al., with a sample of 80 infants, used an experimental formula with a fraction of MFGM rich in proteins that also had a lower energy and protein content compared to a standard formula. At 12 months of age, a significantly higher cognitive score was observed in the treated group compared to the control group, according to the Bayley scale [33]. There were no significant differences between the treated group and the control group of breastfed infants. However, after these results, these infants did not show a better cognitive score at 6.5 years of age compared to the infants who were fed standard formula [40].

In the randomized clinical trial by Li et al. [37], it was observed in a sample of 223 infants, that adding MFGM and bovine lactoferrin in supplemented formulas led to better results at the cognitive, language and motor levels, evaluated with Bayley's scale at 12 months of age. However, few differences were detected at the cognitive level at 18 months of age, and better scores were only observed in language. In the COGNIS cohort, the studies evaluated the effects of infant formula enriched with components of the fatty globule membrane (MGG), LC-PUFA and prebiotics and probiotics ($n = 85$) on the neurocognitive, immune development and growth of the child, compared to babies who received a standard infant formula ($n = 85$) or were breastfed ($n = 50$), at 18 months. When the effect of the type of milk ingested on neurodevelopment at 4 months was assessed, no differences were observed between children taking standard formula or supplemented formula [36]. Regarding the results obtained in the long term (2.5 and 4 years of age) on psycho-emotional and behavioural disorders (Child Behavior Checklist) and on language development (assessed with the language test (PLON-R)), respectively, it was observed that children fed with the enriched formula had lower scores in affective problems and higher scores in language than those fed with the standard formula, respectively [38, 39]. In this scenario, we cannot attribute these benefits exclusively to MFGM, but rather to the combined effects of the symbiotics with the MFGM and LC-PUFAs in the formula used in the COGNIS cohort.

These observations lead to the conclusion that adding MFGM and/or the complex lipids provided with the MFGM fraction to infant formulas is beneficial to cognitive development, although these benefits are observed mainly in the short term and not in the long term.

Conclusions

This review examines the effect of the different nutritional components incorporated into infant formulas on the cognitive development of full-term infants and children. The most researched supplements were initially and mainly long-chain polyunsaturated fatty acids (LC-PUFA), some proteins and recently, milk fat globule membrane (MFGM) and its components. We did not find any studies that linked probiotics and prebiotics with cognitive function. Studies of IF supplementation with LC-PUFA only observed some positive effects on some specific cognitive functions or no effect on overall cognitive function. Therefore, in general, there is no evidence that there is a clear and consistent benefit of supplementing IF with LC-PUFA for the development of child cognitive function evaluated in the short term, in infancy, in the stage of 4 to 6 years old, or in children older than this age. The few studies that have modified the amount of protein in IFs and determined the effect on cognitive function also did not find any improvement in neuropsychological tests in children.

Recent studies of IF supplementation with MFGM and/or the complex lipids provided with the MFGM fraction appear to have obtained a beneficial response for the cognitive development of children in the short term, but no long-term effects have been observed.

Further studies are needed to confirm the safety of nutritional supplementation in IFs and to obtain more evidence to clarify the effects of these compounds on the development of cognitive function in term children.

Acknowledgements The authors are grateful to the journal for the invitation to write this review and URV English Service for the review of the manuscript.

Author Contributions The authors' contributions are as follows: formulated the research question, V. A.; designed the study, V. A.; search strategy, V. A., C. B., C. J.; selected studies, A. D., L. I.; writing—original draft, V. A.; writing—review & editing, V. A., C. J., C. B., J. C. All authors read and approved the final manuscript.

Declarations

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Conflict of Interest The authors do not have any potential conflicts of interest to disclose.

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•• Of major importance

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