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Nutritional Interventions to Enhance Intellectual Development: Strategies, Key Nutrients, and Mechanisms

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ABSTRACT: Intellectual development is a critical aspect of human growth. While a variety of factors contribute to intellectual development, nutritional interventions have emerged as a feasible approach to promoting intellectual development. However, a knowledge gap remains in consolidating the latest findings that connect nutritional interventions with the promotion of intellectual development. Thus, in this review a bibliometric analysis of research was conducted on the influence of nutritional interventions on intellectual development from 2002 to April 2025. It examined the methodologies employed in this field, evaluated the impact of various nutrients on cognitive development, elucidated the mechanisms by which nutritional interventions affect cognitive development, and forecasts future research trends in this domain. The results may steer the exploration of novel nutrient factors for enhancing functional intelligence, as well as provide a theoretical basis for further in-depth studies on the mechanisms underlying intellectual development.

Keywords: Brain development; Learning and Memory; Nutrition; Bibliometric

1. Introduction

Intellectual development is a complex physiological process influenced by genetic, environmental, social, educational and other factors. Fundamentally, it is rooted in genetic factors [1-3]. However, it will also be profoundly influenced by other factors, including the living environment [4], exercise [5-7], diet [8], economic level [9], level of participation in social interactions [10] and education(Figure 1) [11].

Interestingly, studies have revealed that the dietary patterns may affect the intelligence level to a certain extent. For instance, studies have shown that residents of coastal areas where fish and seafood are the staple foods may show higher levels of intelligence due to higher intake of Omega-3 fatty acids. Recent studies confirmed the association between the Mediterranean diet, which is characterized by its emphasis on olive oil, vegetables, fruits, and fish, and increased levels of cognitive function [12]. In contrast, the Western diet,

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characterized by its reliance on ultra-processed, refined carbohydrates, high sugar, and high fat, has been shown in studies to hurt cognitive performance [13].

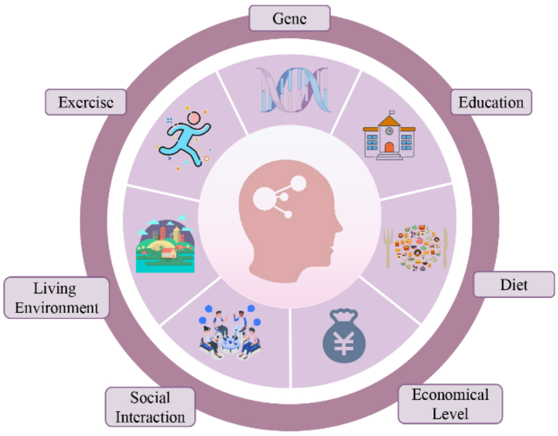

Figure 1 Factors affecting intellectual development.

In recent years, a number of studies have examined the relationship between dietary patterns and intellectual development. While several reviews have discussed the regulatory effects of dietary interventions on the intellectual development [14-16], however, the majority have employed a narrative approach and have not incorporated systematic bibliometric analyses. Therefore, in this review, the impact of nutritional interventions on fostering intellectual development was systematic bibliometric analyzed by summarizing literature reporting nutritional intervention to promote intellectual development. Through methodological evaluation and thematic mapping, we identify predominant experimental approaches, emerging trends, and mechanistic pathways within this field. These findings not only inform future research trajectories but also establish theoretical foundations for developing cognitive-enhancing functional foods.

2. Method

2.1 Data sources and search strategies

In this review, the Web of Science Core Collection was chosen as the data source with indexes being selected as SCI-EXPANDED and SSCI. The search was performed with following search terms: TS=(improve learning and memory OR improve cognitive development)) AND TS=(brain development OR Neuronal development)) AND TS=(offspring OR infant OR pup OR young)) NOT TS=(Alzheimer's disease AND neurodegenerative diseases AND aging AND impairment AND disorder AND Alzheimer Disease)))) NOT WC=(Psychology AND Education & Educational Research)) AND DT=(Article)) AND LA=(English)). Studies published from 2002 to the present were included in this search. The data retrieval time of this paper is up to April 8, 2025.

Inclusion criteria: (1) Human studies and animal studies exploring nutritional interventions to enhance mental development; (2) Published between 2002 and 2025; (3) English language literature; (4) article type Article; (5) full text available.

Exclusion criteria: studies not related to the topic of this review, such as interventions of environment, exercise, stress, drugs.

Literature was searched and screened by 2 researchers, and the consensus was achieved by resolving the disagreements through the mediation of a senior researcher.

2.2 Data analysis

In this review, VOSviewer (version 1.6.20), and Origin (version 2020) were used to perform a bibliometric analysis.

3. Result

3.1 Research characteristics

A total of 823 documents were initially retrieved, of which 127 were finally included after removing duplicates and entries that did not meet the criteria for reviewing this paper. The research methodology and data screening process are shown in Figure 2.

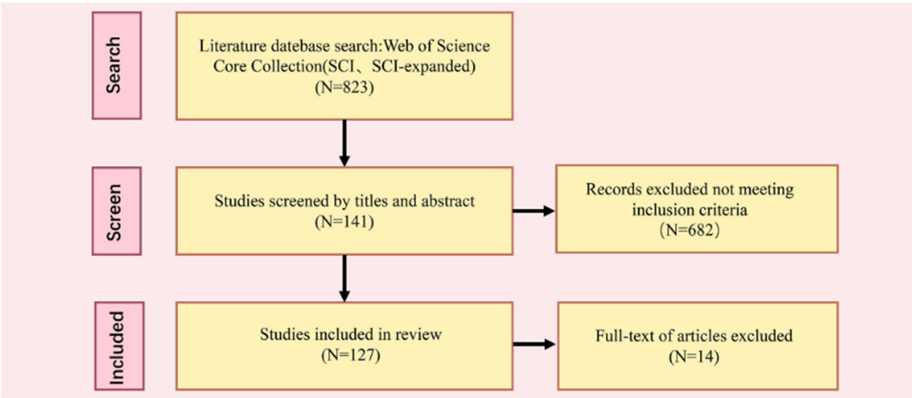

Figure 2 Flowchart of the data screening process.

The 127 articles used in this bibliometric analysis were authored by 879 scholars from 308 institutions in 43 countries, published in 78 journals, and cited by 5917 citations from 1643 journals. The number of publications in this field since 2002 is shown in Figure 3. There has been a consistent rise in the number of studies in this field since 2002. Notably, from 2017 onward, the overall number of publications has seen a substantial increase compared to all prior years.

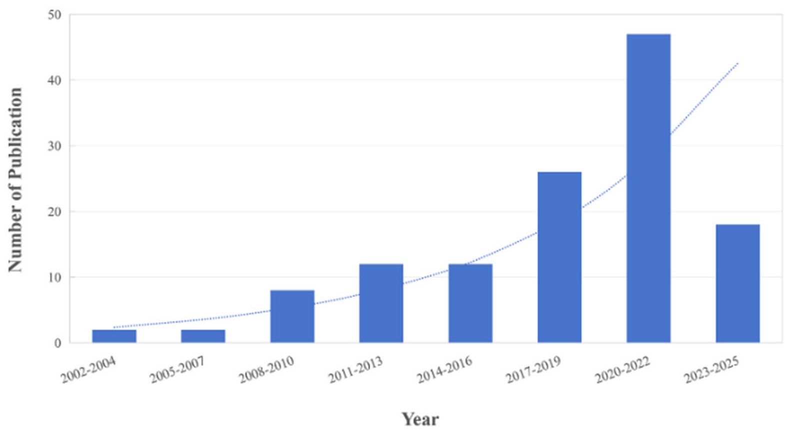

Figure 3 Annual trends in the number of publications.

By analyzing the volume of publications, citation counts, and the average citations per article, the academic influence of a country can be evaluated [17]. As illustrated in Figure 4 and Table 1, American scholars lead in both research output (40 publications, accounting for 31.5%) and academic impact (an average of 43.15 citations), reflecting exceptional productivity coupled with sustained scientific influence in this field. China is the second largest contributor with 23 publications, but with a relatively low citation rate of 7.61. The data indicated that while Chinese researchers have demonstrated significant productivity in this domain, this productivity has not translated into commensurate scientific impact. Despite lower publication volumes than China, articles from Australia, England, and Spain demonstrate higher mean citation rates. a greater average number of citations. Taking China and the United States as examples, several factors may explain the substantial disparity in citation rates between the two countries. A comparative analysis of the literature reveals that United States tends to emphasize highly persuasive human studies, which are predominantly published in high-impact journals (mainly Q1 quartile). Notably, high-impact journals are often characterized by rigorous peer-review processes and broad international readerships, which may contribute to the higher citation rates. Besides, according to the VOSviewer analysis, the "Total link strength" of the United States reaches 30, while that of China is only 13. This data indicates that the United States has more connections with other countries. Therefore, more frequent international collaboration by US scholars may also contribute to the greater visibility and higher citation rates of their published papers.

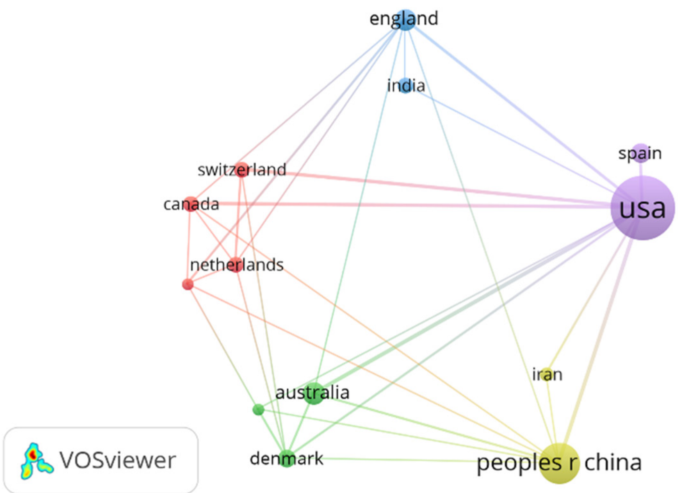

Figure 4 The cooperation network visualization map of countries. The larger the circular node in the figure, the more the number of papers. The node line indicates the correlation strength, and the thicker the line, the more cooperative the papers between the two countries. Node colors represent different clusters.

Table 1 The top 5 countries in the number of published papers and their citation numbers and the number of average citations.

	Country	Publications	Citations	Average Citation/ Publication
1	The United States	40	1726	43.15
2	China	23	175	7.61
3	Australia	11	274	24.91
4	England	10	383	38.30
5	Spain	9	392	43.56

To provide insights into the prevailing research trends within a specific academic domain, the co-occurrence of high-frequency keywords (>5 times) was next investigated [18]. Figure 5 presents the keyword co-occurrence network following synonym consolidation, revealing five thematic clusters. The red clusters encapsulate the mechanisms and responses associated with learning memory. The brain can consolidate spatial memory via the mechanism of long-term potentiation (LTP), while responses such as oxidative stress may disrupt this process, consequently impacting the capacity for learning and memory [19]. The green clusters focus on critical nutrients that are inextricably linked to neurodevelopment when the study is preterm, such as polyunsaturated fatty acids (PUFAs), docosahexaenoic Acid (DHA), arachidonic acid (AA), and breastfeeding. The blue clusters indicate that the supplementation of essential nutrients (sialic-acid, phospholipids, gangliosides), critically enhances cognitive performance during learning and memory processes [20]. The yellow clusters signify investigative approaches for assessing infant learning and memory capacities, predominantly utilizing human double-blind trials and animal in vivo models. The purple clusters emphasize that the abundant nutrients in infant formula can provide strong support for growth and development. While keyword clusters form distinct groups, they exhibit substantial interconnectivity. Each cluster represents a concentrated reflection of a specific research direction or theme. For example, studies on premature infants and infants have different focuses. Figure 4 illustrates the five interconnected clusters forming an integrated knowledge network.

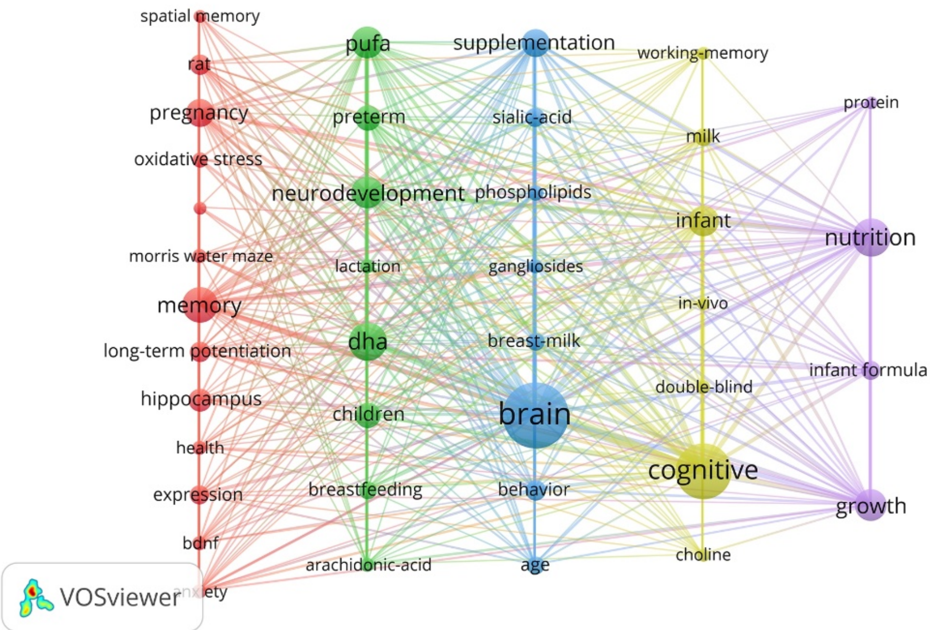

Figure 5 Keyword co-occurrence cluster graph. The larger the circle, the higher the frequency of the keyword occurrence. Different colors in the figure represent different thematic clusters. Lines between keywords indicate correlations between different topics. (Red: Neuroplasticity Mechanisms in Memory Formation; Green: Early Neurodevelopmental Nutrition; Blue: Essential Nutrients for Cognitive Enhancement; Yellow: Cognitive Assessment Methodologies; Purple: Nutritional Support in Infant Formula.)

3.2 Classification of types of studies on nutrient interventions to modulate intellectual stimulation

3.2.1 Choice of Experiment Type

In general, the literature can be divided into two categories: animal studies and human studies. Specifically, there were 80 animal studies (62.99%), as shown in Table 2. Human studies comprised 47 instances (37.01%), as detailed in Table 3.

Table 2 A summary of animal studies.

Nutrient	Type of animal	Behavioral experiment	Conclusion	Reference
PUFA （fish oil）	Wistar rats	OFT, EPM, FST, OLT	FO supplementation during critical periods of brain development attenuated anxiety-like and depressive-like behaviors and cognitive dysfunction induced by Obx.	[110]
PUFA (Linum usitatissimum)	Wistar rats	MWM	Flaxseed during perinatal and postweaning periods improves spatial memory to the detriment of growth.	[111]
PUFA (AA)	Sprague Dawley rats	Water Maze Test, RR	Maternal AA supplementation and training positively influence learning outcomes.	[112]
PUFA	Pigs	Recognition of the mother's faeces, Back test, A hidden door test	Sow diet influenced the DHA content in the piglet brains, but there was no clear effect of sow diet on piglet behavior.	[113]
PUFA （omega-3 fatty acids）	C57BL/6 mice	OFT, NOR, LDT, SPT, TCT	Higher paternal intake of n-3 PUFAs in preconception may help to maintain optimal brain development and function in the offspring, and further raise the possibility of paternal nutritional intervention for mental health issues in subsequent generations.	[114]
PUFA （omega-3 fatty acids）	Sprague Dawley rats	OFT, rotarod/accelerate task, Passive Avoidance Test	Perinatal omega-3 supplementation exerts a long lasting beneficial effect on the rotarod performance indicating improvement in balance and motor coordination and, possibly, in the functioning of pathways governing this task.	[115]
PUFA （omega-3 fatty acids）	Wistar albino rats	MWM	Improved dentate gyrus-LTP and enhanced MWM performance in healthy pups from healthy dams treated with Omega-3 fatty acids during pregnancy and breast-feeding period.	[116]
PUFA （omega-3 fatty acids）	C57BL/6 mice	MWM, OFT, Y-Maze Test, Nest-building test	Omega-3 supplementation can improve cognitive function in offspring after prenatal lead exposure.	[117]
PUFA （omega-3 fatty acids）	Wistar rats	MWM, RAM	Prenatal supplementation with omega-3 polyunsaturated fatty acids improved cognitive performance in offspring at 3 months of age.	[118]
PUFA （nucleotides）	C57BL/6 mice	MWM, OFT, Shuttle-box	Maternal supplementation of exogenous nucleotides could ameliorate prenatal ethanol-induced learning and memory deficits in C57BL/6J mice to some extent.	[61]
PUFA (linolenic acid)	Sheep	NOR, T-Maze, Stimulus test, ACTH challenge, Novel arena test,	A diet rich in linseed given to gestating and lactating goats seems to increase the attention/exploration of their kids at 11 days without affecting their learning ability.	[119]
PUFA （DHA, UMP）	Sprague Dawley rats	Water Maze, Rotarod apparatus and testing	Giving DHA plus UMP can ameliorate memory deficits associated with rearing under impoverished conditions.	[120]
PUFA （DHA）	Pigs	OFT, Object Recognition test	Perinatal DHA supplementation may increase exploratory behaviors, improve recognition memory, enhance fiber tract integrity, and alter brain functional organization in offspring at weaning.	[33]
PUFA （DHA）	C57/BL6 mice	No	DHA can promote neurite development, synaptogenesis and expression of synapsins and glutamate receptors, improving glutamatergic synaptic transmission.	[34]
PUFA	C57BL/6 mice	No	ω-3 fatty acid DHA promotes synaptic connectivity and cortical processing.	[35]

（DHA）				
PUFA（DHA）	Wistar rats	No	The exposure of pregnant women to Pb might similarly affect DHA content in human milk, and hence DHA-mediated brain cognitive ability.	[121]
PUFA (alpha-linolenic acid but no EPA or DHA)	C57BL/6 mice	EPM, NOR, Grip strength, Accelerating rotarod, Auditory cued fear conditioning	Supplemental PUFAs attenuate the cognitive impairments caused by PAE.	[122]
PUFA (walnuts)	Wistar rats	No	A diet enriched with African walnuts during early development induced changes predictive of cognitive improvements and enhanced stress-response signalling, plasticity, and neural resilience in rat offspring.	[123]
PUFA, Vitamins（fish oil, folic acid）	Wistar rats	MWM	Fish oil supplementation during pregnancy improved cognitive performance and maintained glucose levels into adulthood.	[124]
PUFA, Vitamin（omega-3 fatty acids, vitamin B12）	Wistar rats	MWM, RAM	Prolonged vitamin B12 deficiency adversely influences learning and cognition.	[52]
PUFA, Mineral（omega-3 fatty acids, iodine）	Sprague Dawley rats	MWM, Y-maze test, Motor coordination test	Iodine and n-3 FA rescues not only the loss of neurotrophic support, but also salvages motor coordination, memory and learning.	[67]
Vitamin（choline）	Sprague Dawley rats	No	Early choline can mitigate some long-term effects of ethanol exposure on hippocampal inflammation, which may contribute to improved hippocampal function.	[56]
Vitamin（choline）	Wistar rats	NOR	Prenatal supplementation with choline accelerates the development of long-term memory in rats.	[54]
Vitamin（choline）	C57BL/6 mice	locomotor activity, Accelerating rotarod, neurological battery, contextual and cued fear conditioning	Postnatal choline supplementation attenuates some behavioral deficits in Mecp21lox mice.	[55]
Vitamin（choline）	Sprague Dawley rats	No	Prenatal choline supplementation causes elevations of NGF concentration in the hippocampus of juvenile and adult rats as well as a transient elevation of NGF concentration in the frontal cortex of juvenile rats.	[57]
Vitamin（choline）	Wistar rats	No	Maternal choline supplementation on the first day of gestation until PND 21 improves brain development and cognitive function.	[125]
Vitamin (folic acid /FA）	C57BL/6 mice	MWM, OFT, EPM, NOR, FST, Y-Maze	Gestational FA administration has a therapeutic effect that improves cognition and reduces depression and anxiety.	[60]
Vitamin（vitamin E）	Sprague Dawley rats	MWM	Prenatal and postnatal TRF supplementation improved cognitive function development in male progeny rats.	[126]
Vitamin (α-tocopherol）	Sprague Dawley rats	MWM, Multiple Y-Maze Test, CFC, LDT, Activity cage	α-Tocopherol maternal treatment influences explorative drive in adult offspring.	[127]
Vitamin（vitamin B12）	Lister Hooded rats	No	B-12–supplemented rats may have enhanced sensitivity to sensory stimulation, but do not provide evidence supporting the hypothesis of decreased neural activity due to B-12 supplementation.	[128]
Vitamin (vitamin D)	C57BL/6 mice	No	Vitamin D supplementation before pregnancy improves offspring cognitive performance in AMA mice.	[129]
Vitamin, Mineral (choline, iron)	Iron-Deficient Mouse Hippocampal Neurons	No	Iron repletion significantly improved mitochondrial respiration, ATP production rates, overall dendrite complexity (100–180 µm from the soma), and dendrite and branch lengths compared with untreated ID neurons.	[58]

Mineral (zinc）	Wistar rats	Water Maze Test, T-Maze, Hole Board Test	The dose-dependent improvement of spatial learning and memory in rat pups after pre- and postnatal zinc administration.	[66]
Breast Milk	Pigs	OFT, An in-cage cognition test	Dietary fat source influences the plasma and to a lesser degree the hippocampal lipidome and is unable to improve on IUGR-induced brain structural and functional impairments.	[130]
Breast Milk	Pigs	T-Maze	Dietary phospholipids and gangliosides improved spatial learning and affected brain growth and composition in neonatal piglets.	[131]
Breast Milk	C57BL/6 mice	OFT, EPM, NOR, TCT	Early life exposure to a diet with lipid droplets that mimic the supramolecular structure of those in mammalian milk may improve adolescent growth and alters brain function in both socially and individually housed mice.	[132]
Breast Milk	Sprague Dawley rats	MWM	cGP treatment/supplementation during infancy moderately improved adulthood spatial memory.	[133]
Breast Milk	Sprague Dawley rats	OFT, NOR, LDT	Maternal cGP supplementation improves memory in developing offspring.	[134]
HMO （OF, 2'-FL）	Pigs	NOR	Dietary OF and OF + 2'-FL differentially improve cognitive performance and affect olfactory bulb structural development and hippocampal gene expression.	[135]
HMO （2'-FL）	C57BL/6 mice, Sprague Dawley rats	i.e. Skinner box	Dietary 2’-FL affects cognitive domains and improves learning and memory in rodents.	[136]
HMO, BMOS (2'-FL, Lacto-N-neotetraose)	Pigs	NOR	HMO and BMOS had distinct effects on brain structure and cognitive performance.	[137]
HMO (2'-FL）	Lister Hooded rats	MWM, NOR, Y-Maze Test	Oral administration of 2′-FL exclusively during lactation enhanced cognitive abilities, not only in childhood but also in adulthood.	[138]
HMO (3'-SL）	C57BL/6 mice	MWM; Y-Maze; NOR	Supplementation with 3′-SL during the growth period can promote cognitive and memory development in the brain.	[139]
MFGM	Sprague Dawley rats	T-Maze, Passive Avoidance	Early postnatal provision of MFGM, especially in the presence of a growth insult, can stimulate early neurobiological development leading to long-term improved cognitive outcomes.	[140]
MFGM	Sprague Dawley rats	Palmar grasp, Negative geotaxis, Cliff avoidance, Ear twitch, Eyelid twitch.	Addition of bovine MFGM to formula promotes reflex development and alters brain phospholipid and metabolite composition.	[141]
MFGM	Sprague Dawley rats	MWM, NOR, T-Maze	SIA and phospholipids in the MFGM have positive effects on behavior and are involved in up-regulation of genes in the hippocampus.	[142]
MFGM	Pigs	T-Maze	Adding 1.74 g MFGM per 100 g diet can significantly improve neonatal piglets’ learning and memory abilities.	[143]
MFGM	Sprague Dawley rats	MWM, NOR, Neurological reflexes（righting reflex and cliff avoidance）	Maternal MFGM-PL supplementation can promote neurodevelopment.	[144]
MFGM (polar lipids)	Wistar rats	MWM, OFT, EPM, NOR, RR	Memory specific functional benefits of long-term dietary PL during post-natal brain development.	[145]
Sialic acids (Sia) （Neu5Ac, 6'-SL）	Sprague Dawley rats	NOR, Y-Maze Test with Blocked Arm Test	Providing Sia during lactation, especially as 6′-SL, improves memory and LTP in adult rats.	[146]
Sia (edible bird’s nest)	ICR mice	MWM	maternal administration of EBN during the pregnancy and lactation periods can improve the spatial learning performances in the offspring.	[20]

Sia (edible bird's nest)	Sprague Dawley rats	MWM	Maternal administration of EBN improved the learning and memory function of the offspring.	[97]
Sia	Sprague Dawley rats	MWM, Shuttle-box	Maternal Neu5Ac supplementation during pregnancy could effectively promote the brain Neu5Ac content of the offspring and enhance their cognitive performance, but Neu5Ac had no such effect on rat pups while directly supplemented with Neu5Ac.	[49]
Sialyllactose	Pigs	T-Maze	Oligosaccharide-enriched whey with sialyllactose improved spatial cognition.	[147]
Protein (milk osteopontin)	Pigs	T-Maze	Dietary supplementation with OPN above basal bovine milk levels induced minor improvements in gut structure and systemic immunity without any effects on cognitive performance.	[68]
Protein (alpha-lactalbumin)	Pigs	OFT, T-Maze	WPC-supplementation resulted in pronounced beneficial effects on the growth and functional development of body and organ systems, gut, immunity and structural brain development.	[69]
Protein (bovine milk OPN)	C57BL/6 mice	Passive Avoidance Test	bmOPN up-regulates expression of endogenous OPN and myelination-related proteins in the brain and promotes cognitive development.	[70]
Amino acid (taurine)	Sprague Dawley rats	MWM, OFT, Grip strength test	Taurine can restore abilities of learning and memory in young rats exposed to VOCs.	[78]
Amino acid (taurine)	BALB/c mice	EPM, RR, OFT, LDT, NOR, SPT, The cheeseboard maze, The Barnes maze, Step-down test, Y-Maze	TAU supplementation during maternal gestational and weaning time enhanced memory function and locomotor activities in mice offspring.	[77]
Carotenoids （lutein, zeaxanthin, β-carotene and so on）	monkeys	No	Carotenoid formula supplementation influences functional brain development.	[80]
Carotenoids （curcumin）	C57BL/6 mice	EPM, NOR, Spontaneous alternation Y-Maze Test, T-maze alternation test	Curcumin treatment ameliorated cognitive deficits and reversed the pro-inflammatory response induced by alcohol.	[79]
Others （Camellia sinensis）	Swiss Webster mice	EPM, Righting Reflex, Rotating Reflex, Active Avoidance Reflex (Shuttle-Box Test), Cliff Avoidance Reflex, Locomotion Activity Reflex, Equilibrium Reflex,	C. sinensis confers protective effects against perinatal nicotine-induced neurobehavioral alterations, tissue injury, and oxidative stress in mice newborns.	[86]
Others (spirulina)	Sprague Dawley rats	OFT, EPM, RR, LDT, SPT, Forelimb grip strength test, Active avoidance, Barnes maze	Spirulina consumption may assist in restoring the behavioral and cognitive skills in protein malnourished F1 rats.	[82]
Others （steroid hormones）	Wistar rats	Y-maze, RAM, Bradford dye-binding-Protein assay	Steroid hormones play an important role in the spatial learning and memory formation by means of protein synthesis in different lobes of the brain.	[148]
Others (caffeine)	Sprague Dawley rats	MWM	Caffeine may interfere with oligodendrocyte maturation and with synaptic function, conferring protection to neonatal brain tissue against damage caused by hypoxia and ischemia.	[83]

Others (caffeine)	Sprague Dawley rats	MWM	Caffeine improved long-term cognitive function in neonatal rats.	[149]
Others (caffeine)	ICR mice	MWM, NOR, RR	Caffeine can ameliorate cognitive impairment.	[150]
Others (caffeine)	Bees	Y-maze	Caffeine has marked cognitive effects in this species	[151]
Others (creatine)	Sprague-Dawley albino rats	No	Maternal supplementation with creatine can affect morpho-functional maturation of neurons in developing hippocampus and promotes permanent effects on synaptic plasticity in adult offspring,	[81]
Others (synbiotics, Glutamine)	Pigs	T-maze	Preterm pigs supplemented with Bifidobacterium breve, galacto- and fructo-oligosaccharides, and L-glutamine showed enhanced neuronal and immunological development.	[152]
Others (ethanolic extract from bulbs of Cipura paludosa)	Wistar rats	Social recognition task, Inhibitory avoidance task	Chronic treatment with the EE of C. *paludosa* reduced the long-lasting short-term learning and memory deficits induced by prenatal MeHg-exposure.	[85]
Others (virgin coconut oil)	rats	MWM	VCO significantly improved memory and learning function.	[153]
Others (safflower oil)	Wistar rats	OFT, NOR	Maternal intake of safflower oil could change neonate reflex parameters, promote improvement of cognitive development in adolescence, improve antioxidant enzymatic and non-enzymatic defenses in the hippocampus.	[154]
Others (obestatin)	rats	MWM	Neuroprotective effects of Obestatin on alcohol-related behavioral, biochemical and molecular deficits.	[155]
Others (frankincense)	Wistar rats	MWM	Maternal injection of frankincense during gestation and lactation periods improved spatial memory retrieval.	[84]
Others (BSC)	Wistar rats	MWM, EPM, LDT	BSC supplementation during post-natal brain development improved learning and memory, independent from anxiety.	[156]
Others (quercetin)	Wistar rats	Y-maze	Maternal QE supplementation can prevent working and recognition memory impairments in adult MIA offspring.	[157]
Others (Moringa oleifera Leaf Extract)	Sprague Dawley rats	Y-maze	EEMO supplementation can improve neurocognitive and spatial memory capacities in protein-deficient offspring.	[158]
Others (Lactobacillus paracasei GF027)	Sprague Dawley rats	EPM、OFT	Lactobacillus paracasei GF027 promotes systemic growth and cognitive function by regulating gene expression and activating gut-brain axis pathways.	[159]

Abbreviation: BSC, Beta Serum Concentrate; BMOS, Bovine Milk Oligosaccharides; CFC, Contextual fear conditioning, EPM, Elevated Plus Maze Test; FST, Forced Swim Test; HMO, Human Milk Oligosaccharides; LDT, Light-dark Test; MWM, Morris Water Maze; MFGM, Milk fat globule membranes; NOR, Novel Object Recognition; OFT, Open Field Test; OLT, Object Location Behavioral Test; RR, Rota Rod Test; RAM, Radial Eight Arm Maze Test; SPT, Sucrose Preference Test; TCT, The Three-chamber Test.

Table 3 A summary of human studies.

Nutrient	Type of Research	Duration/ Object of evaluation	Assessment methods	Result/Conclusion	Reference
PUFA （PUFA, AA, DHA）	RCT	2013.10-2020.2	Bayley-III	Higher dietary intakes of total PUFAs, DHA and AA during the first year of life are associated with better neurodevelopmental outcome in terms of motor and cognitive function at 12 months CA.	[160]
PUFA （DHA, AA）	RCT	for 6 months	Bayley-III	Daily supplementation with 200 mg of DHA and 200 mg of AA for 6 months resulted in no improvement in cognitive development and early measures of executive function vs placebo, and may have resulted in negative effects on language development and effortful control in certain subgroups of children.	[39]
PUFA （DHA）	RCT	from 18 to 22 week of pregnancy until delivery, assessed at age 5 years	MSCA, BASC-2, K-CPT	Prenatal exposure to DHA may contribute to improved sustained attention in preschool children.	[36]
PUFA （DHA）	RCTs	within the first 3 days of enteral feeding until 36 weeks' postmenstrual age	Bayley-III	/	[161]
PUFA （DHA）	RCTs	within the first 3 days of enteral feeding until 36 weeks' postmenstrual age	Bayley-III	Enteral DHA supplementation did not result in improved attention in infants born preterm at 18 months corrected age.	[38]
PUFA （DHA）	RCTs	Five-year/5 y	WPPSI-IV, a measure of inhibitory control (fruit stroop)	In infants less than 29 weeks gestation, supplementation with enteral DHA at an estimated intrauterine dose did not improve behavioral function at 5 years of age.	[162]
PUFA (DHA, choline, uridine-5-monophosphate)	RCT	for 2 years/2 y	Bayley-III	/	[42]
PUFA (DHA, choline, uridine-5-monophosphate	RCT	for 2 years/2 y	Bayley-III	Dietary supplementation of neonates at risk of neurodevelopmental impairment is feasible,but no statistically significant neurodevelopmental advantages were identified for the treatment group compared to controls.	[40]
PUFA (DHA, choline, uridine-5-monophosphate	RCT	for 2 years/2 y	Bayley-III	No statistically significant neurodevelopmental advantage for the treatment group versus the comparison group. However, treatment group cognitive and language advantage were of clinically meaningful magnitude.	[41]
PUFA (DHA, choline, uridine-5-monoph	RCT	term-equivalent age (or at latest 3 weeks post-term) up to 12 months CA	Bayley Scales of Infant Development III , Ages and Stages Questionnaire 4 (ASQ-4), and Parent Report of Children’s Abilities –	/	[163]

osphate			Revised (PARCA-R)).		
PUFA （DHA, AA）	RCT	started 1 week after birth and lasted until discharge from the hospital (on average, 9 weeks) / at 6 months of age	the Ages and Stages Questionnaire and event-related potentials	Supplementation with docosahexaenoic acid and arachidonic acid for very preterm infants fed human milk in the early neonatal period was associated with better recognition memory and higher problem-solving scores at 6 months.	[37]
PUFA (complex milk lipids)	RCT	begins at the time of recruitment (11–14 weeks of gestation) and ends when the baby is born	Bayley-I	CML supplementation with MFGM from the end of the first trimester had no effect on fetal growth.	[164]
PUFA （infant formula enriched with bioactive compounds, LC-PUFA（DHA and ARA）, MFGM, probiotics and prebiotics）	RCT	during their first 18 months of life/at four years old	PLON-R	The functional compound-enriched infant formula seems to be associated with beneficial long-term effects in the development of child’s language at four years old	[165]
PUFA (fish）	Cohort Study	at 17 years	WCST, CVLT, CANTAB, W-JII, Achievement Test, measures of problematic behaviors	Ocean fish consumption during pregnancy is important for the health and development of children and that the benefits are long lasting.	[166]
PUFA （fish oil）	RCT	at 12 and 24 months corrected age	Bayley-III	Parenteral nutrition using a mixed lipid emulsion containing fish oil did not improve neurodevelopment of ELBW infants at 12 and 24 months corrected age.	[167]
PUFA （LCPUFA）	RCT	12 month feeding study, 6-week weaning study, 4-to 6-month weaning study	a two-step problem solving task	LCPUFA-supplementation improves means-end problem solving.	[168]
PUFA （LNS）	RCT	at 4–6 y of age	a cognitive factor score based on a test battery adapted from several standard tests, fine motor score (9-hole pegboard test), social-emotional difficulties (SDQ)	Provision of LNS during the first 1000 d of development improved behavioral function, but did not affect cognition at preschool age in this setting.	[169]
PUFA, Protein	retrospective cohorts	at 2 and 5.9 years corrected age	Bayley-III, WPPSI-III-	In extremely preterm born infants, postnatal protein intake seems important for white matter development but does not necessarily improve long-term cognitive and motor development.	[170]
Vitamin （vitamin B12）	RCT	at 6 and 12 months of age	Bayley-III	Vitamin B12 supplementation (50 μg vitamin B12 per day) from early pregnancy through 6 months postpartum did not improve the growth and neurodevelopment of the baby.	[171]
Vitamin （vitamin B12）	prospective study	aged 4 years	WPPSI-IV, NEPSY-II	Maintaining an adequate level of maternal vitamin B12 during early pregnancy contributes to improved performance in childhood working memory at 4 years	[51]

				of age.	
Vitamin （vitamin B12）	Pune Rural Intervention in Young Adolescents trial (PRIYA)	from preconception until delivery/at 24–42 months of age	Bayley-III	Pre-conceptional vitamin B12 supplementation improved maternal B12 status and offspring neurodevelopment at 2 years of age.	[21]
Vitamin （vitamin B12）	RCT	for 12 months	Bayley-III	Vitamin B12 supplementation in young children at risk of vitamin B12 deficiency resulted in an improved metabolic response but did not affect neurodevelopment, growth, or hemoglobin concentration.	[172]
Vitamin （vitamin B12）	RCT	for 12 months	WPPSI-IV, FSIQ	Providing 2 μg of vitamin B12 for a year in infants at risk of vitamin B12 deficiency does not improve preschool cognitive function	[173]
Vitamin（phosph atidylcholine）	RCT	from 18 weeks gestation through 90 d postpartum/ at 10 and 12 months of age	Short-term visuospatial memory, long-term episodic memory, language development, and global development	Phosphatidylcholine supplementation of pregnant women eating diets containing moderate amounts of choline did not enhance their infants' brain function.	[174]
Vitamin （vitamin D）	RCT	unit at week 24 and until 1 week after birth/at ages 0 to 6 years	Bayley, age of motor milestone achievement (Denver Developmental Index and World Health Organization milestone registration), language development (MacArthur-Bates Communicative Development Inventories), general neurodevelopment at age 3 years (Ages and Stages Questionnaire), and emotional and behavioral problems at age 6 years (Strengths and Difficulties Questionnaire)	Maternal high dose vitamin D3 supplementation during the third trimester of pregnancy did not improve neurodevelopmental outcomes in the offspring during the first 6 years of life.	[62]
Mineral （iodine）	a community-based cluster-randomised effectiveness trial	between 25 October 2010 and 13 October 2013/at 20–29 months	Bayley Scales of Infant and Toddler Development	The introduction of iodised salt contributes to children's higher urinary iodine concentration and mental development.	[63]
Mineral （iodine）	permutation tests	age between 6 and 14 years	WPPSI-III	Does the iodized salt therapy of pregnant mothers increase the children IQ.	[65]
Mineral （iodine）	RCT	for 3 years/at 36 months of age	Bayley-III	Maternal iodine supplementation with 150 μg/d during lactation may have a beneficial effect on child cognitive development, no evidence of either improved or delayed neurodevelopmental outcomes in children whose mothers received iodine supplements at doses higher than recommended.	[175]
Mineral （iodine）	RCT	at ages 1, 2, and 5.7 years	Bayley-III, WPPSI-III, BRIEF-P	Daily iodine supplementation in mildly iodine deficient pregnant women was associated with small	[176]

				negative effects on maternal thyroxine concentrations, but did not affect child development.	
Mineral （iron）	RCT	at 3 months postintervention (month 3), and after a further 9 months follow-up (months 12).	ERPs	In Bangladeshi children with >40% anemia prevalence, iron or MNP interventions alone are insufficient to improve neural indices of habituation.	[177]
Mineral （MNP）	A retrospective cohort study	for 3 months	Motor development（the WHO Multicentre Growth Reference Study guidelines）	Provision of low-iron dose MNPs on alternate days is associated with lower prevalence of anaemia, stunting, and increased motor development achievements.	[64]
Mineral （MMN）	RCT	at 12 years	UNIT, the counting Stroop test	No differences in IQ or executive function at 12 years between children whose mothers received multiple micronutrient supplementation in pregnancy and those who did not.	[178]
Mineral, Vitamin (MMN)	RCT	at age 9–12 years	general intellectual ability, declarative memory, procedural memory, executive function, academic achievement, fine motor dexterity, and socioemotional health	Maternal MMN had long-term benefits for child cognitive development at 9–12 years of age.	[179]
Mineral, Vitamin	cohort study	aged 10-12	WPPSI-IV	Improvement in iron-rich or iron-fortified foods complementary feeding may produce better adolescent cognitive development outcomes.	[180]
Breast milk	cohort study	at least 3 months	the Mullen Scales of Early Learning (Mullen, 1995), WPPSI-V	Significantly improved overall myelination in breastfed children accompanied by increased general, verbal, and non-verbal cognitive abilities compared to children who were exclusively formula-fed.	[181]
Breast milk	A cross-sectional study	a minimum of 3 months	/	Infant breastfeeding is associated with improved developmental growth in late maturing white matter association regions, and extended breastfeeding duration is associated with improved white matter structure and cognitive performance.	[182]
Breast milk	cohort study	breast fed longer than 6 months/at 18 months of age:	Bayley-III	Longer duration of breast feeding was associated with increased scores in cognitive, language and motor development at 18 months of age.	[183]
Breast milk	a temporal brain network study	32.20 ± 0.89 weeks of gestational age to (40.00 ± 1.31 weeks, range 39–44 weeks	/	Beyond a prominent temporal small-world topology, breastfed infants showed improved temporal brain network architecture at both global and regional levels, which are also correlated with the percentage of breastfeeding.	[44]
Breast milk	a prospective cohort study	infants breastfed for 4 months or longer, at age 1, 2 and 3 years.	IMQ	Breastfeeding for 4 months or longer was associated with improved developmental outcomes for children aged one to 3 years.	[45]
Breast milk	RCT	during the last trimester to 12 weeks postpartum/at 30 months old	Bayley-III	MMS with breastfeeding support during late pregnancy and early postpartum was associated with improvements in neurodevelopment in children at 30 months old.	[184]

Breast milk	cohort study	at 48 months	BSID-III, KBIT-2	Nutrients in breast milk may improve general child cognition, while nursing infants directly at the breast may influence memory.	[46]
Breast milk	An observational study	at 32 months	/	Breastmilk-fed infants had greater regional gray matter development and increased regional gray matter function compared with formula-fed infants at near term-equivalent age.	[27]
Breast milk	cohort study	breastfed 6 months or more, at 2 years	ASQ, PARCA-R, the short version of the MacArthur Communicative Development Inventory for language abilities, questions on language acquisition,	VPT children fed with breast milk had both improved nonverbal and verbal cognitive development at 2 years.	[185]
Breast milk	partial least squares correlations (PLSC)	children (range: 2—15 years) , adults (range: 20—60 years)	PLSC, Network Analysis	During childhood, eBF appears to promote white matter development. In adulthood, eBF may play a protective role that reduces neural loss associated with physiological aging	[186]
Breast milk		aged 12–36 months	Dominican Infant Development Measurement System (SIMEDID), INAIPI's Initial Health and Nutrition Assessment Form	After accounting for age and sex at birth, children who were ever breastfed exhibited significantly better overall developmental outcomes than those who were not.	[187]
Breast milk, MFGM	Multicenter Study	starting from 21 d (±7 d) until 4 months of age	the serum metabolome and fecal microbiota	Supplementing MFGM enhanced in formula-fed infants while facilitating fatty acid oxidation and ketogenesis, a feature that may favor brain development.	[188]
MFGM	RCT	for 12 months	Bayley-III	MFGM supplementation in early life supports adequate growth, increased serum gangliosides concentration and improves some measures of cognitive development in Chinese infants.	[189]

Abbreviation: ASQ, The Ages and Stages Questionnaire; BASC-2, the Behavioral Assessment System for Children-Second Edition; BRIEF-P, Behavior Rating Inventory of Executive Function; Bayley-I, Bayley scales of infant and toddler development-First Edition; Bayley-III ,Bayley scales of infant and toddler development-Third Edition; CVLT, the California Verbal Learning Test; CANTAB, the Cambridge Neuropsychological Test Automated Battery; ERPs, Auditory Event Related Potentials; FSIQ, Full Scale Intelligence Quotient; IMQ, the Infant/Child Monitoring Questionnaire; K-CPT ,the Conners' Kiddie Continuous Performance Test; KBIT-2, the Kaufman Brief Intelligence Test- Second Edition; MSCA, the McCarthy Scales of Children's Abilities; MNP, micronutrient powders; MMN, Multiple Micronutrient; NEPSY-II, Neuropsychological Assessment of Development-second edition; PLON-R ,the Oral Language Task of Navarra-Revised; PARCA-R, the Parent Report of Children's Abilities-Revised; RCT, Randomized Controlled Trial; SDQ, Strengths and Difficulties Questionnaire; UNIT, Universal Non-verbal Intelligence Test; WPPSI-III, the Wechsler Preschool and Primary Scale of Intelligence-Third Edition; WPPSI-IV, the Wechsler Preschool and Primary Scale of Intelligence-Fourth Edition; WPPSI-V, the Wechsler Preschool and Primary Scale of Intelligence-Fifth Edition, WCST, the Wisconsin Card Sorting Test; W-JII, the Woodcock-Johnson.

The analysis revealed that the predominant animal model utilized in experimental research is the rodent models, specifically mice and rat. Studies using rodent models accounted for 82.5% of the animal experimental literature, as shown in Figure 6 (a). This phenomenon stems from rodents' shared anatomy and physiology with humans, combined with their practical advantages such as cost-effectiveness, abundance, and high survival rates. In the choice of rodents, the researchers favored the use of rats for the study. Among the rats, Sprague Dawley (SD) rats were the most utilized (25 times, 37.87%), followed by Wistar rats (18 times, 27.27%). It should be noted that one paper involves both SD rats as well as C57BL/6 mice in the study. In addition, two papers did not explicitly mention the type of rats. In the searched literature, mice were selected in the study in 20 papers. C57BL/6 mice were most widely used (15 articles), followed by ICR mice (2 articles), Swiss Webster mice (1 article), and BALB/c mice (1 article). In addition to the rodent models, pigs were also utilized as experimental subjects in eleven studies, making them the second most frequently employed model after rodents. Moreover, three studies used monkeys, sheep and bees as animal models.

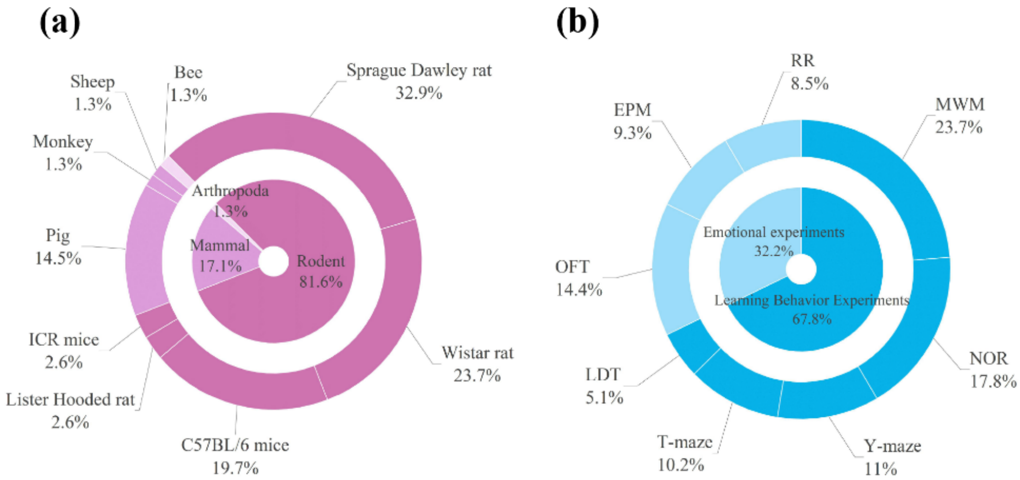

Figure 6 Statistical analysis of assessment methods of intellectual development. Note:(a) classification and proportion of animal models; (b) classification and proportion of behavioral experiments.(EPM: Elevated Plus Maze Test; MWM: Morris Water Maze; LDT: Light-Dark boxes Test; NOR: Novel Object Recognition; OFT: Open Field Test; RR: Rotating Reflex.)

Human studies usually encompass the observation and intervention of a large number of people over a long period to assess the effects of nutritional interventions on the intellectual development of the population. Population-based trials can be classified into two primary categories: Randomized Controlled Trials (RCTs) and Cohort Studies. The RCTs was used to hypothesize a causal relationship between nutritional interventions and intellectual development by designing control and experimental groups to observe differences in effects before and after nutritional interventions. Cohort studies track a specific group of individuals (a cohort) over time, monitoring their outcomes after exposure to nutritional interventions. The analysis indicates that population studies were conducted more frequently in 2018 (9 articles, 19%), 2020 (8 articles, 17%), and 2021 (8 articles, 17%). Human studies have predominantly focused on fatty acids (17 articles, 36%), breast milk and its main constituent groups (14 articles, 29%), and minerals (8 articles, 17%) as core nutritional interventions. This may be due to the following reasons. Firstly, these nutrients (fatty acids, breast milk, and minerals) are basic nutrients. Conducting human studies on these essential nutrients holds practical significance as it can contribute to the development of more scientifically-based dietary guidelines and nutrition policies.

Furthermore, they provide crucial support for improving infant health and child growth and development. Thirdly, extensive animal research on these nutrients has established safety profiles and ethical feasibility, thus making them more suitable for human studies.

3.2.2 Choice of assessment method

A major manifestation of intellectual development is the ability to learn and memory. Human learning and memory abilities can be reflected in intuitive ways such as reading and writing. Therefore, the primary evaluative method utilized in human studies is the Intelligence Scale. The assessment of subjects depends on their age. Infants (1 month to 42 months) are usually applied to the Bayley Scales of Infant and Toddler Development (BSID), with the BSID-III being widely used [21]. Preschool and elementary children (2 years and 6 months through 7 years and 7 months) are frequently applied to The Wechsler Preschool and Primary Scale of Intelligence (WPPSI) [22], with the most commonly used ones being WPPSI-IV.

In animal studies, it is challenging to directly apply the aforementioned method. Therefore, the learning memory ability of animals needs to be measured by observing behavioral changes in external stimulus [23]. Figure 6 (b) demonstrates three principal behavioral paradigms: learning and memory behavioral experiments, emotional behavioral experiments, and motor behavioral experiments.

In the learning and memory behavior experiment, the Morris Water Maze (MWM) is the most widely adopted [24]. Among the 80 animal studies, 28 utilized the Morris Water Maze (MWM), highlighting its prominent position as the classical behavioral experiment for assessing spatial learning and memory in animals. Three other articles also applied the Water Maze Test though not MWM. In addition to MWM, other commonly utilized methodologies in behavioral experiments on learning and memory include Novel Object Recognition (NOR) (21 articles), Y-maze (13 articles), T-maze (12 articles) and Light-Dark boxes test (LDT) (6 articles). Similarly, we also observe that conventional behavioral experiments were used in the articles, including the Shuttle-box test, Passive Avoidance Test, Radial Arm Maze, Barnes Maze, etc.

Cognitive assessment requires multidimensional evaluation encompassing learning and memory performance, emotional regulation, and motor functions. Therefore, in addition to learning and memory experiments, a number of research experiments on intellectual development could also be supplemented by emotional behavior experiments to determine whether animals are anxious and detect their spontaneous behavior ability. For example, the Open Field Test (OFT) and the Elevated Plus Maze Test (EPM) were applied 17 and 11 times respectively in the articles we retrieved. OFT and EPM have been frequently employed as behavioral experiments related to anxiety [25]. The open field test (OFT) does not elicit strong reactions in the experimental animals and has little impact on their behavior. Commonly, the OFT is the initial test conducted in a series of behavioral experiments. Although EPM involves only changes in light and dark stimuli and does not require injurious stimuli, it has greater environmental stress stimuli compared to OFT experiments. Therefore, the anxiety of experimental animals can be further verified based on the OFT experiment. The literature suggests that the results of the EPM experiment should align with those of the OFT experiment, allowing for mutual corroboration [26]. Some research articles also analyze the impact of depressive emotions on experimental animals. Therefore, literature also presents behavioral testing indicators directly related to depression, such as the Forced Swim Test (FST). Interestingly, these behavioral experimental methods demonstrate cross-species validity beyond rodent models. For example, pigs have successfully implemented OFT, NOR, and T-maze.

Recent advances have introduced novel experimental paradigms that integrate cutting-edge neuroimaging techniques with genetic manipulation methodologies. Both in animal and human studies, researchers reveal intellectual development variations through behavioral experiments and intelligence scales, while also incorporating Magnetic Resonance Imaging (MRI) to examine its effects on brain structure development [27]. MRI has revealed structural alterations in the brain that correspond to cognitive and behavioral changes identified through experimental assessments and intelligence metrics. These findings corroborate and enhance our comprehension of the interplay between brain structure and function throughout the developmental process. In particular, MRI is predominantly utilized in research involving mammalian models, such as pigs and monkeys. Among these studies, eight focused on the use of MRI in pigs.

3.3 Regulation of dietary nutrition on intellectual development

3.3.1 The role of diet in promoting intellectual development

Brain development and intellectual performance are directly affected by the amount and type of the nutrients consumed. Particularly, the early 1,000 days of life are the foundation for neurodevelopment [28]. The nutrition provided during this critical period impacts brain growth and shapes cognitive abilities in later life. The subsequent discussion will focus on the role of nutrients in intellectual development. Meanwhile, eating habits and diet quality also impact intellectual development. For instance, a high-energy diet may impair learning and memory [29]. A study simulated rats exposed to Western dietary behaviors during lactation to investigate the impact of cafeteria diet (CD) on the learning and memory capacity of offspring [30]. The results suggest that providing CD to pregnant rats during lactation leads to increased energy intake and decreased protein intake. This leads to enhanced learning and memory capacity in male offspring but hampers the females. Interestingly, a recent study showed that a soft diet led to cognitive decline in the offspring [31]. Consequently, early consumption of hard foods may enhance chewing ability and improve cognitive performance [32].

3.3.2 The role of various nutrients in promoting intellectual development

Various types of nutrients have been found to regulate intellectual development. The analysis of the retrieved literature revealed that the key nutrients included fatty acids, vitamins, minerals, breast milk, etc. Figure 7 illustrates the distribution of studies on each nutrient type. Fatty acids are the most extensively researched nutrient, with 35 articles (27.56%) focusing on them. The number of studies was followed by breast milk (34 articles, 26.78%), vitamins (17, 14.29%), minerals (8, 6.72%), proteins (3, 2.52%) amino acids (2, 1.68%), carotenoids (2, 1.68%), multi-nutrient action (4, 3.36%), and other substances (17, 13.39%).

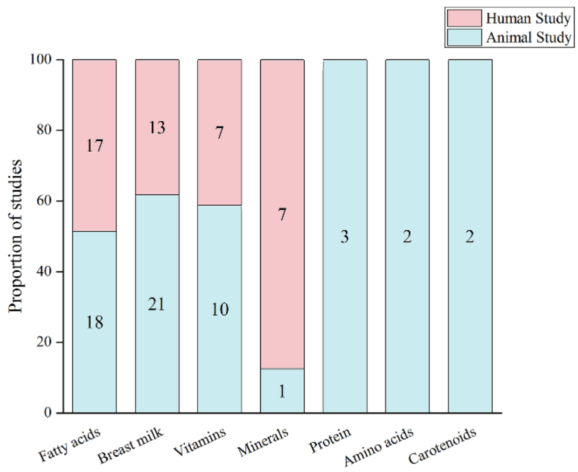

Figure 7 The proportion of each nutrient in animal studies and human studies. The numbers in the figure represent the number of specific articles.

3.3.2.1 Fatty acids

Fatty acids are essential nutrients for the development of the brain's nervous system. Particularly, polyunsaturated fatty acids (PUFAs) have garnered significant attention in the study of mental development. There were 35 papers related to dietary supplementation with fatty acids, including 18 animal studies and 17 human studies. This aligns with the results from our bibliometric analysis, showing Docosahexaenoic Acid (DHA), Polyunsaturated Fatty Acids (PUFAs), and Arachidonic Acid (AA) frequently appeared as keywords. Current research has revealed that dietary intake during pregnancy and the early postnatal period plays a significant role in the growth and development of the offspring. Numerous studies in animal models have demonstrated that supplementing unsaturated fatty acids during pregnancy can improve the learning and memory capacities of offspring [33-35]. A Mexican population-based randomized controlled trial confirmed these findings [36]. Nevertheless, the impact of fatty acid intake on enhancing mental development during the early postnatal period remains contentious based on feedback from human studies. A randomized, double-blind, placebo-controlled study revealed that infants supplemented with docosahexaenoic acid and arachidonic acid in breastfed preterm infants had better recognition memories and achieved higher problem-solving scores [37]. However, these findings contrast with two other studies [38, 39], which reported no significant enhancement in cognitive performance with DHA supplementation in preterm infants. Similarly, DHA did not significantly improve neurodevelopment in newborns at risk for neurodevelopmental disorders [40-42]. In summary, research on prenatal dietary intervention has shown positive effects on intellectual development in most studies. However, most postnatal research has concentrated on preterm infants or neonates with neurodevelopmental disorders. Since the amount of DHA accumulated in their mothers is already much lower than that of full-term infants, preterm infants must receive adequate amounts of DHA and other essential nutrients during the postnatal period to support their intellectual development. The findings from human studies indicate that additional validation of the postnatal stage is required.

3.3.2.2 Breast milk

Breast milk is considered the optimal nutrition for infants and young children [43], which significantly impacts cognitive development. This is primarily attributed to its high concentration of bioactive, including proteins, carbohydrates, lipids, vitamins, salivary acids, taurine, and various immunologically active components and enzymes. This biochemical complexity has prompted extensive investigation into breast milk, milk fat globule membranes, sialic acids, breast milk oligosaccharides, and other bioactive of breast milk on the mental development. Additionally, the interaction between mother and child during breastfeeding is crucial to this developmental process. There are 34 studies on breast milk, comprising 21 animal studies and 13 human studies. Firstly, breastfed children performed better on intelligence tests than formula-fed children, and the results of the intelligence tests were consistent with the characterization of brain regions scanned through MRIs [27, 44]. Moreover, continuing breastfeeding for 4 months or more is associated with improved mental development of the offspring [45]. Secondly, skin-to-skin contact (SSC), eye contact, and various interactions between the mother and child during breastfeeding facilitates the development of the infant's perceptual, emotional, and neural systems. These interactions serve as positive stimuli for the infant's brain. Pang's study showed that infants who were breastfed directly via maternal contact had better performance on various memory assessments compared to those who were fed expressed breast milk from a bottle [46].

The Milk Fat Globulin Membrane (MFGM), abundant in breast milk, contains over one hundred types of proteins. The search yielded eight articles about MFGM, all suggesting that early supplementation with MFGM may enhance offspring's learning and memory abilities.

Human milk oligosaccharides (HMOs) are a class of complex oligosaccharides that are abundant in breast milk in free form, constituting the third largest component of breast milk. Increasing evidence suggests that HMOs can enhance brain development. Fucosyllactose (FL) and sialyllactose (SL), such as 2'-fucosyl lactose (2'-FL) and 6'-sialyl lactose (6'-SL), are often the main chain of HMO. A total of four studies were conducted on 2 '-FL, two of which used pigs as models and the other two used mice as models. All four studies demonstrated dietary supplementation with 2'-FL enhances LTP and improves cognitive function through the regulation of synaptic plasticity.

Sialic acid, a key components of breast milk, provides essential support for early brain development [47] and the refinement of an infant's immune system. Sialic acid can be present in free form or combined with oligosaccharides to form SL [48]. Six studies reported that providing free or conjugated sialic acid to mothers during pregnancy could enhance offspring's cognitive development. Bian's study found that maternal supplementation with Neu5Ac during pregnancy enhanced cognitive performance, but direct supplementation with Neu5Ac had no such effect on rat pups [49]. Oliveros' research further compared the efficacy of free salivary acid (Neu5Ac) and bound salivary acid (6'-SL), revealing that supplementation with 6'-SL resulted in superior performance on specific cognitive measures.

3.3.2.3 Vitamins

At present, various vitamins have been shown to contribute to animals' cognitive function, learning, and memory abilities, as well as significantly affecting the development of the nervous system. The search data showed that 17 studies were on vitamins. The most studied are vitamin B12 (7 studies) and choline (6 studies), as well as folic acid, vitamin E, vitamin D, and other vitamins.

Vitamin B12 is pivotal in synthesizing neurotransmitters and regulates brain development, effectively preventing neural function defects and enhancing concentration in infants and young children. Vitamin B12 deficiency in mothers during pregnancy and lactation can impact the brain development and cognitive function of infants and children [50]. Therefore, continuous administration of vitamin B12 during pregnancy and lactation can help improve the neurodevelopment of offspring, as observed in the seven studies we reviewed [21, 51]. Notably, a study even suggested that combined vitamin B12 and n3 fatty acids may bring beneficial effects on improved brain function in offspring up to third-generation offspring [52].

Choline is an essential nutrient required for early development [53]. Six studies investigated the impact of dietary choline supplementation on cognitive development. All these studies illustrated that choline enhances cognitive development [54] and alleviates behavioral deficits [55] in offspring by improving hippocampal function [56, 57] and stimulating dendritic growth [58].

The importance of folic acid during pregnancy has been widely acknowledged. It has been suggested that folic acid supplementation during pregnancy may improve the neurodevelopment of infants by lowering serum homocysteine (Hcy) levels, which leads to a decrease in inflammatory factor levels in the body. Evidence from animal studies suggests that both high and low maternal folate levels during pregnancy correlate with changes in gene methylation linked to neurodevelopment and learning memory functions in male offspring [59]. A research study investigated the effects of folic acid supplementation on pregnant women. Maternal folic acid supplementation was shown to activate hippocampal BDNF-related pathways and promote hippocampal neurogenesis resulting in enhanced synaptic plasticity and synaptic transmission that correlate with improved cognitive performance and emotional regulation during pregnancy [60] .

Vitamins exhibit a dose-dependent effect in animals. Moderate intake of vitamins can promote mental development and neurological well-being in animals, but excessive intake may result in toxic or adverse reactions. An animal study and a human study assessed the effects of vitamin D supplementation on the neurodevelopmental outcomes of offspring. Both studies indicated that fetal vitamin D acquisition greatly relies on maternal placental transport. Consequently, the vitamin D levels in fetuses and newborns are profoundly determined by the mother's vitamin D status. Thus, maintaining sufficient maternal vitamin D levels is crucial for the intellectual development of offspring [61]. However, high maternal intake of vitamin D during pregnancy does not further enhance the offspring's mental development and could potentially lead to adverse effects [62].

3.3.2.4 Mineral

Eight articles explored the impact of trace mineral elements on mental development, specifically focusing on iodine, iron, and zinc. The majority have concentrated on iodine, partly due to the widespread global prevalence of iodine deficiency disorders (IDD). As a result, studies on minerals are often conducted in regions vulnerable to deficiencies, such as Ethiopia [63, 64]. Researchers have discovered that animals with mineral deficiencies often show declines in behavior and cognition. For example, animals with iron deficiency may show reduced activity levels, longer reaction times, and impaired learning abilities. Animals lacking zinc may encounter challenges in attention and memory retention. Iodine deficiency can result in thyroid dysfunction, potentially impacting the growth and cognitive development of offspring [65]. Enhancements can be observed after supplementing the corresponding deficient nutrients [63, 66]. Similarly, the effects of minerals on mental development are often interconnected with other nutrients, environmental factors, and so forth. Two human studies have investigated the effects of combining iron and choline [58] and iodine with n-3 fatty acids [67]. Additionally, three animal studies have examined the improvement of intellectual development with the complex micronutrient MMN. Research has shown that combined supplementation of nutrients can exert a synergistic effect, promoting their absorption and utilization of minerals, and eventually enhance intellectual development.

3.3.2.5 Proteins

Three animal studies investigated the impact of proteins on enhancing cognitive development. Two studies utilized pigs as the animal model [68, 69], while one employed C57BL/6 mice [70]. The studies investigated the effects of α-lactalbumin (α-Lac) and milk bone bridging protein (bmOPN) on cognitive development, respectively.

Osteopontin (OPN) is an acidic protein with high glycosylation and phosphorylation that is abundant in early human milk and plays critical roles in neonatal development [71]. While bovine milk-derived OPN (bmOPN) is commercially added to formula, its current concentration (9 mg/L) [72] remains substantially lower than breast milk levels. Studies have shown that bmOPN supplementation reduces developmental differences between formula and breastfed infants by mimicking the composition of breast milk [73, 74]. Mechanistically, bmOPN shares conserved integrin-binding domains with murine OPN, enabling activation of cell signaling pathways through conserved integrin binding sites, which provides theoretical and experimental support for formula addition [70]. However, preterm pig studies reveal limited efficacy: OPN-supplemented dairy diets only marginally improve intestinal morphology and systemic immunity, with no significant neurostructural or functional enhancements [68]. Alpha-lactalbumin (α-LAC), the predominant whey protein in human milk, exhibits significant amino acid sequence homology with its bovine counterpart [75]. Experimental evidence confirms that α-LAC confers multifaceted benefits, including promotion of infant growth, gut microbiota regulation, and immune function enhancement [69]. Collectively, these investigations indicate that formula optimization through strategic emulation of breast milk's critical bioactive constituents holds clinical promise, though their direct neurodevelopmental impacts warrant deeper mechanistic exploration to establish causal efficacy pathways.

3.3.2.6 Taurine

There were 2 animal studies on taurine's effect on enhancing mental development. Taurine, the most abundant sulfur-containing free amino acid in humans [76], promotes intellectual development through multiple molecular mechanisms. In the normal development model [77], taurine supplementation (0.5%-1%)

from maternal pregnancy to offspring maturity can significantly improve the cognitive function and emotional behavior of offspring, increase the level of ATP in brain and hippocampus mitochondria, and enhance the efficiency of energy metabolism. In the model of cognitive impairment induced by environmental toxins (VOCs) [78], taurine can effectively restore the learning and memory ability of pups by inhibiting oxidative stress, balancing neurotransmitters, activating NMDA receptors and up-regulating the expression of BDNF/NMDAR1 protein, and the effect of 1% supplemental dose is better. Accumulating evidence demonstrates that taurine's mechanism of action encompasses diverse pathways including mitochondrial optimization, antioxidant defense, synaptic plasticity modulation, and toxin antagonism. These findings establish taurine not only as a crucial nutritional component in early neurodevelopment (particularly critical during infancy when endogenous synthesis is underdeveloped), but also reveal its therapeutic potential in pathological contexts. This understanding provides critical scientific evidence for designing prenatal nutritional supplements and developing cognitive intervention strategies for pediatric populations.

3.3.2.7 Carotenoids

Carotenoids contribute to cognitive development through their antioxidant, anti-inflammatory, and neuroprotective properties. Carotenoids are mainly represented by beta-carotene, lutein, and curcumin. Two animal studies explored the effects of carotenoids on intelligence development. A study in mouse models has demonstrated that curcumin can improve cognitive deficits [79]. Another study used fMRI to observe that supplementation with a carotenoid formula, which included lutein, beta-carotene, and other carotenoids, facilitated the development of brain networks in a monkey model [80].

3.3.2.8 Others

As scientific inquiry and technological advancements progress, researchers have increasingly explored novel substances that are expected to be promising avenues for enhancing cognitive development. Besides mainstream nutrients, research reports on new nutrients such as Creatine [81], Spirulina [82], Caffeine [83], Frankincense [84], Ethanolic extract [85], and Camellia sinensis [86] are increasing. Notably, most of these studies have only been conducted in animal models. Therefore, human studies may be needed to further explore the effects of these novel substances on promoting cognitive development.

3.4 Mechanism of nutritional intervention in promoting intellectual development

The relationship between nutritional intake and enhancements in learning and memory capabilities is a multifaceted process. In the subsequent discussion, we will summarize the mechanism by which nutritional intervention regulates intelligence development. This summary aims to provide a theoretical framework for understanding the potential interaction mechanism of nutrition intervention on intelligence development.

The exploration of mechanisms primarily relies on animal experimental models [87]. In animal studies, physiological and biochemical indicators such as oxidative stress level, neurotransmitter level and key protein level are often measured based on behavioral experiments [88]. The specific indicators for each level are illustrated in Figure 8.

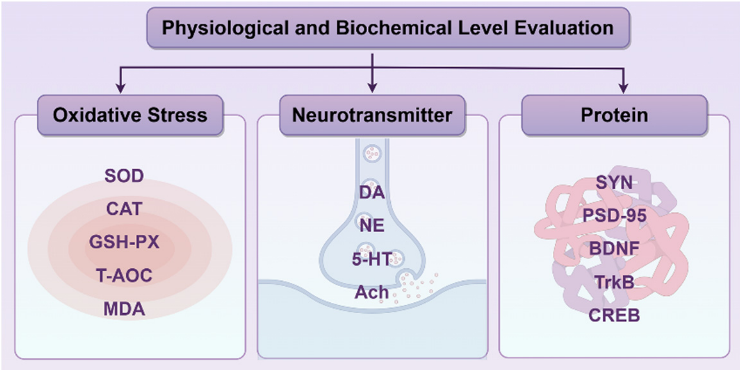

Figure 8 Three physiological and biochemical evaluation levels of experimental animals during the study of intellectual development.(SOD: Superoxide Dismutase; CAT:Catalase; GSH-PX:Glutathione Peroxidase; T-AOC: Total Super Oxidedismutase; MDA: Malondialdehyde; DA: Dopamine; NE: Norepinephrine; 5-HT:5-Hydroxytryptamine; Ach:Acetylcholine; SYN:Synaptophysin; PSD-95:Postsynaptic Density Protein-95; BDNF:Brain-Derived Neurotrophic Factor; TrkB: Tyrosine Kinase Receptor B; CREB: cAMP-Response Element Binding Protein.)

The brain plays a central role in intellectual development. Particularly, the hippocampus is a critical region in the central nervous system [89] that is vital for learning and memory processes. On the one hand, the capacity for learning and memory is highly correlated with the number of neurons in the hippocampus. The hippocampus can be divided into several regions, including Cornu Ammonis 1 (CA1), Cornu Ammonis 2 (CA2) and Cornu Ammonis 3 (CA3) [90], and Dentate Gyrus (DG), as illustrated in Figure 9. It has been discovered that the sialic acid found in Edible Bird's Nest (EBN) can significantly increase the number of neurons in the CA1, CA2, CA3, and DG regions, thereby enhancing the spatial learning abilities of the offspring [20]. Furthermore, dendrites serve as the initial points for information transfer between neurons [91]. As such, dendritic density is a crucial factor in neuronal connectivity and information transmission. The intake of DHA [34]and choline [58] can stimulate the growth of dendrites, improve the overall complexity of dendrites and stabilize synaptic structure, thus improving memory ability. In studies, the brain tissue samples of experimental animals are usually stained by staining pathological means such as HE staining, Nissl staining and Bielschowsky silver staining to observe the above changes.

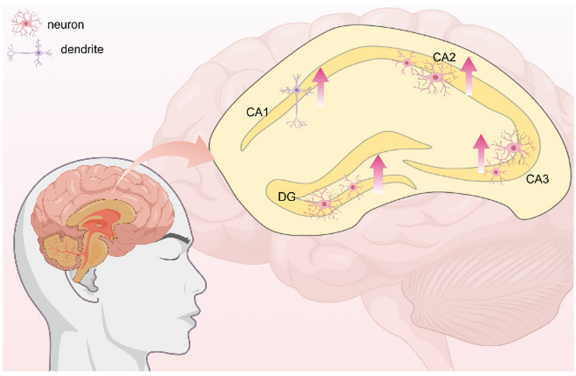

Figure 9 Location map of the hippocampal regions. The arrows in the figure indicate that when the number of neurons increases or the density of dendrites increases, hippocampus development is promoted. (CA1: Cornu Ammonis 1; CA2: Cornu Ammonis 2; CA3: Cornu Ammonis 3; DG: Dentate Gyrus.)

The brain is a complex and vulnerable organ in the body, the redox state of the hippocampus is closely related to learning and memory. The redox status can be reflected by measures of relevant oxidative stress markers in brain tissue or blood can be measured. such as malondialdehyde (MDA), superoxide dismutase (SOD), total super oxidedismutase (T-SOD), glutathione (GSH), Glutathione peroxidase (GSH-PX) and catalase (CAT). In dietary nutrition, vitamins with antioxidant properties, particularly vitamin C and vitamin E, are essential for protecting the developing brain from oxidative stress. A total of 2 papers explored the effects of vitamin E on offspring and examined alpha-tocopherol (α-T) and tocotrienol fractions (TRF), respectively. Both studies showed that vitamin E intake during early or critical periods of life protects the growing brain from oxidative stress, exerts neuroprotective properties, and facilitates the development of cognitive function.

Neurotransmitters are chemicals released from synaptic vesicles by presynaptic membrane to transmit signals from one nerve cell to another, affecting brain function and behavior. Studies have shown that nutrient intake can affect the synthesis and release of neurotransmitters. For instance, tryptophan is a precursor of 5-HT [92], a neurotransmitter that plays a crucial role in regulating mood [93]. Tyrosine (TYR) acts as a precursor of dopamine (DA) and norepinephrine (NE), impacting mood, motivation, and cognitive functions [94]. Choline is a crucial precursor for acetylcholine synthesis, with its intake directly influencing the synthesis of Acetylcholine (ACh). ACh plays a significant role as a neurotransmitter in the central cholinergic nervous system [95]. Particularly, the central cholinergic system is an important component of the neural circuitry involved in learning and memory in animals. The synthesis, decomposition and release pathways of ACh are shown in Figure 10. The study found that the intake of nucleotides can reverse the levels of acetylcholinesterase (AChE) in mice exposed to ethanol environment, thereby improving the learning and memory deficits induced by prenatal ethanol exposure in their offspring [61].

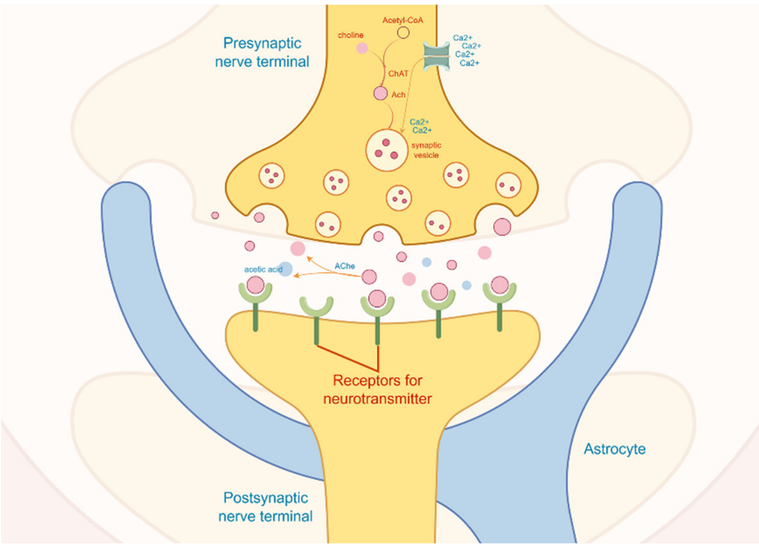

Figure 10 Pathways of acetylcholine (Ach) synthesis, decomposition and release in the acetylcholinergic system. (Ache: acetylcholinesterase; ChAt: Choline acetyltransferase.)

Synaptic plasticity-associated protein expression levels may serve as biomarkers for assessing neurological status and elucidating molecular mechanisms underlying cognitive development. The pathways involved in enhancing intellectual development are mainly related to promoting the growth of brain-derived neurotrophic factor (BDNF), phosphorylation of cAMP-response element binding protein (CREB) and the synthesis of down-streaming memory-related proteins. Supplementation with omega-3 fatty acids and vitamin B12 during pregnancy upregulate BDNF, TrkB, and CREB in the hippocampus and cortex of offspring, contributing to enhanced cognitive performance [96]. Maternal EBN supplementation elevated hippocampal

BDNF levels and enhanced ERK and CREB phosphorylation in offspring, activating the ERK-CREB-BDNF signaling pathway and improving the offspring learning memory function[97]. Figure 11 summarizes the three main pathways for CREB activation[98-100]. Through the CREB pathway, synaptic plasticity can be activated, neural protection can be enhanced, and LTP can be induced [101]. Cognitive development involves intricate biological mechanisms. While the roles of the ERK/CREB, cAMP-PKA-CREB, and CaMKII/CREB/BDNF pathways in intellectual development have been partially elucidated, these pathways represent only a subset of well-characterized regulatory routes. In reality, the molecular basis of cognitive development encompasses a broader signaling network, including complex interactions among identified pathways and other undiscovered ones. Focusing on these core pathways provides critical targets for understanding the molecular framework of cognitive development and lays a theoretical foundation for systematically exploring complex regulatory networks. Future research should identify key regulatory nodes based on classical pathways, while incorporating emerging pathways to break through traditional frameworks and explore novel approaches, thereby constructing a multi-tiered regulatory mechanism for intellectual development.

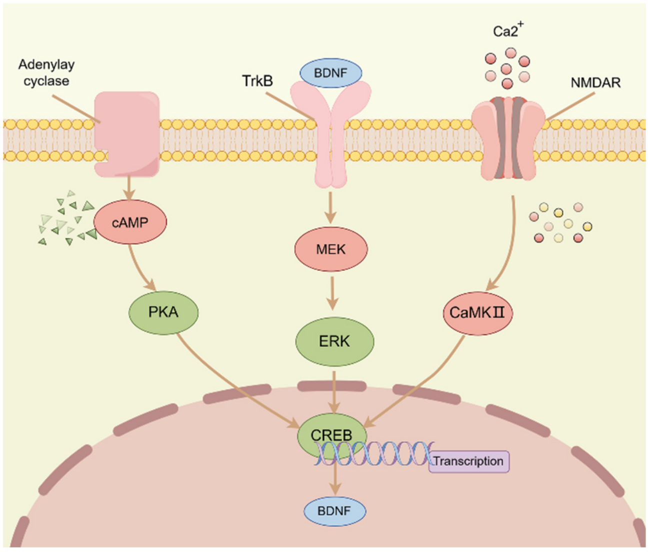

Figure 11 Three key pathways activate cAMP-response element binding protein (CREB). (cAMP: Cyclic adenosine monophosphate; CaMKII: calcium/calmodulin-dependent protein kinase II; BDNF: brain-derived neurotrophic factor; ERK: extracellular signal-regulated kinase; MEK: Mitogen-activated protein kinase kinase; NMDAR: N-methyl-D-aspartate receptors; PKA: protein kinase A; TrkB: tropomyosin-related kinase B.)

The above content summarizes the main mechanisms of nutritional intervention in intellectual development. Critically, due to the complexity and high interactivity of metabolic networks within organisms, the intake of any nutrient does not simply regulate a single level. The underlying mechanisms at play are often achieved through a variety of interrelated and interconnected mechanisms. DHA, a neuroessential omega-3 fatty acid critical for cognitive development [102], is routinely incorporated into maternal-infant formulations [103], and it influences mental development in various ways. On the one hand, DHA is the main component of the brain and retinal cell membranes [104]. Its incorporation into neuronal membranes enhances hippocampal bilayer fluidity, stabilizing the network of neurodevelopmental circuits necessary for learning and memory [105]. On the other hand, DHA is abundant in neuronal and synaptic membranes. DHA critically modulates nerve signaling by enhancing synaptic connections and improving neurotransmitter synthesis [106]. Moreover, DHA exhibits anti-inflammatory and antioxidant properties, mitigating brain inflammation and oxidative stress to protect nerve cells from harm [107].

In recent years, researchers have also started exploring the "gut-brain axis" mechanism of intellectual development, investigating the link between gut microbiota composition and human cognitive, emotional, and memory functions. Based on BSID-III, researchers employed 16S rRNA sequencing, metaproteomic, and metabolomics analyses to elucidate the correlation between infant cognition and gut microbiota. The results showed that the intestinal microbiota of infants with better cognitive ability could enhance the memory of mice and regulate the histidine metabolism of the peripheral blood cortex (PRC), demonstrating a critical role of the gut-brain axis during early neurodevelopment [108]. Following digestion, absorption, and metabolism, the intake of nutrients can impact the composition and abundance of the host gut microbiota. This suggests that mental development mechanisms can be examined through the lens of how dietary nutrients influence the gut microbiota.

4. Conclusion

Intellectual development is a crucial aspect of a child's growth. There exists a strong correlation between nutrient intake and intellectual development [109]. Adequate nutrition forms the basis for a child's intellectual growth. Optimal brain development requires access to a variety of essential nutrients. Here, we have reviewed the literature on nutritional interventions to promote intellectual development. Bibliometrics analysis shows that most of the current studies focus on a single nutrient. In the study of nutrition intervention, animal studies account for a large proportion, and population studies also contributed to the generation of new knowledge in this field. Notably, current research has primarily focused on individual nutrients, potentially overlooking the inherent complex synergistic mechanisms in natural food systems, which typically involve the interactions of multiple aspects such as nutrients, the gut microbiota, and metabolic pathways. In the future, exploring the synergistic effects of multiple bioactive compounds, particularly in population studies, may become a new research hotspot. Future efforts should focus on establishing standardized protocols for assessing multicomponent synergy in functional foods, thereby optimizing formulation applications. From a research perspective, an omics- and multi-component-driven approach is necessary to dissect the mechanisms of nutrient synergies. Building on this foundation, human studies should be enhanced to validate the practical effects of these synergies. Meanwhile, integrating omics data into the development of AI-driven personalized nutrition management systems and promoting the discovery and translation of novel nootropic functional factors remain critical. Additionally, research on nutrient-targeted delivery technologies should focus on achieving precise spatial distribution of nutrients within food matrices through innovative food processing techniques. Take together, this review may help to deepen understanding of the cognitive foundations of intellectual development, providing a pathway for maximizing the cognitive benefits of nutrients and delving deeper into the mechanisms that support brain health.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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