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Influence of diet in special educational needs (SEN) among children and adolescents: a systematic review

A influência da alimentação nas necessidades educativas especiais (NEE) em crianças e adolescentes: uma revisão sistemática

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Abstract

Introduction: Special Educational Needs (SEN) refers to children and adolescents needing additional educational support. Diet during pregnancy and pediatric age can influence the diagnostic and the severity of symptoms in SEN.

Objectives: This systematic review aims to summarize associations between (i) pregnant women's diet and the diagnosis of SEN in children/adolescents; (ii) diet of children and/or adolescents with SEN and the symptomatology and well-being of this group.

Methods: A literature search was carried out on Medline® and Scopus® from March to June 2022, according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (PROSPERO number: CRD42022313235). The following inclusion criteria were considered: children/adolescents ≤ 19 years old; pregnant women's diet/nutrition or children/adolescents' diet/nutrition; diagnostic of SEN in children/adolescents or symptomatology/well-being of children/adolescents with SEN.

Results: Eighty-seven articles were included, making a total of 10 different SEN, in which stands out Attention-Deficit/Hyperactivity Disorder (ADHD) (41 articles) and Autism Spectrum Disorder (ASD) (34 articles). It doesn't seem to exist an association between maternal caffeine consumption and risk of ADHD diagnostic. A protective effect of pregnant multivitamin supplementation in the risk of ASD diagnostic was found. A positive association was found between high-sugar foods and beverages intake and ADHD symptoms, while no association between gluten-free and/or casein-free diet and ASD symptoms was found.

Conclusions: These results are extremely relevant to help to develop guidelines for dietary recommendations for this target population. However, further studies are needed to support these results.

Keywords: special educational needs; systematic review; diet; pediatric age; pregnancy.

Resumo

Introdução: O termo Necessidades Educativas Especiais (NEE) refere-se a crianças/adolescentes que necessitam de apoio educativo adicional. A alimentação durante a gravidez e a idade pediátrica pode influenciar o diagnóstico e a severidade dos sintomas de NEE.

Objetivos: Esta revisão sistemática visa sumariar associações entre: (i) a alimentação da grávida e o diagnóstico de NEE em crianças/adolescentes; (ii) a alimentação das crianças/adolescentes com NEE e a sintomatologia/bem-estar deste grupo.

Métodos: Foi realizada uma pesquisa bibliográfica na *Medline*® e *Scopus*®, de março a junho de 2022, segundo as diretrizes *Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)* (nº PROSPERO: CRD42022313235). Consideraram-se os seguintes critérios de inclusão: crianças/adolescentes ≤ 19 anos; alimentação/nutrição da grávida ou alimentação/nutrição de crianças/adolescentes; diagnóstico de NEE em crianças/adolescentes ou sintomatologia/bem-estar de crianças/adolescentes com NEE.

Resultados: Foram incluídos 87 artigos, num total de 10 NEE diferentes, destacando-se a Perturbação de Hiperatividade/Défice de Atenção (PHDA) (41 artigos) e Perturbação do Espectro do Autismo (PEA) (34 artigos). Não parece existir uma associação entre o consumo materno de cafeína e o risco de diagnóstico de PHDA. Foi encontrado um efeito protetor entre a suplementação materna com multivitamínicos e o risco de PEA. Verificou-se uma associação entre a ingestão de alimentos e bebidas com alto teor de açúcar e os sintomas de PHDA,

enquanto nenhuma associação foi encontrada entre uma dieta isenta de glúten e/ou caseína e a sintomatologia de PEA.

Conclusão: Os resultados apresentados são extremamente relevantes para auxiliar no desenvolvimento de recomendações alimentares deste público-alvo. Contudo, mais estudos são necessários.

Palavras-chave: necessidades educativas especiais; revisão sistemática; alimentação; idade pediátrica; gravidez.

Acronyms List

ADHD - Attention-Deficit/Hyperactivity Disorder

ADHD-RS - ADHD Rating Scale

ASD – Autism Spectrum Disorder

ASQ-P - Conners' Abbreviated Symptom Questionnaires

CARS - Childhood Autism Rating Scale

CBCL - Child Behavior Checklist

CRS - Conner's Rating Scale

DSM-IV - Diagnostic and Statistical Manual of Mental Disorders - 4th Edition

DSM-V - Diagnostic and Statistical Manual of Mental Disorders - 5th Edition

IDEA - Individuals with Disabilities Education Act

PBD – Pediatric Bipolar Disorder

PICOS - Population, Indicator, Comparator, Outcomes, and Study

PRISMA - Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PUFA – Polyunsaturated Fatty Acids

RCT – Randomized Controlled Trial

RR – Relative Risk

SDQ - Strength and Difficulties Questionnaire

SEN – Special Educational Needs

SWAN - Strengths and Weaknesses of ADHD symptoms and Normal Behavior Scale

TS – Tourette Syndrome

Contents

Introduction

Special Educational Needs (SEN) is a legal term used by many countries around the world, referring to children and adolescents with some type of disability, that makes them need additional support to benefit from the school education of the general educational systems made for people with the same age. The definition of SEN is widely variable between countries, which reflects the complexity and diversity of disabilities that can be covered, including mental or physical disabilities, cognitive, or educational impairments[1, 2]. For example, in the Individuals with Disabilities Education Act (IDEA), from the United States Department of Education, 14 disability categories are covered: (1) autism, (2) deaf blindness, (3) deafness, (4) emotional disturbance, (5) hearing impairment, (6) intellectual disability, (7) multiple disabilities, (8) orthopedic impairment, (9) other health impairment, (10) specific learning disability, (11) speech or language impairment, (12) traumatic brain injury, (13) visual impairment, and (14) developmental delay[3]. The Diagnostic and Statistical Manual of Mental Disorders - 5th Edition (DSM-V) is a commonly used tool to attend SEN diagnostic, once the mental disorders included in this manual fit into the SEN categories of the majority of the countries[4].

In the last few years, it has been observed an upward trend of the prevalence of children and adolescents with SEN[5]. Regarding literature, the risk of SEN diagnostic can be influenced by pregnant women' dietary habits. For example, a higher maternal dietary quality index score has been associated with a 13 % decrease of the risk of Attention-deficit/hyperactivity disorder (ADHD) diagnostic in children[6]. Also, maternal exposure to folic acid and multivitamin supplements has been associated with a lower risk of autism spectrum disorder (ASD) diagnostic

in children[7]. In addition, even after a confirmed diagnostic, there is evidence showing that children and adolescent's dietary habits have an impact on symptom's manifestation. As such, a higher intake of sweet deserts, fried food, fast-food, and sugar-sweetened beverages has been related to more severe ADHD symptoms[8-10].

The issue considering the influence of diet on children and adolescents (≤ 19 years old)[11] with SEN has been an increasingly studied topic in the literature in the recent decades[12]. However, as far as the research team is aware, there is still no systematic review that summarizes this information, considering, at the same time, the data available in the literature regarding dietary habits of pregnant women and children/adolescents related to the diagnostic and symptomatology of SEN, respectively. Therefore, it becomes important to systematize this existing information, to contribute towards the establishment of dietary guidelines supporting this group.

Objectives

The main objective of this review was to study the influence of diet in diagnosis, symptomatology, and well-being of children and/or adolescents with SEN. Therefore, the specific objectives were:

(i) To study the association between pregnant women's diet and the diagnosis of SEN in children and/or adolescents;

(ii) To study the association between the diet of children and/or adolescents with SEN and the symptomatology and well-being of this group.

The objectives were transformed in Population, Indicator, Comparator, Outcomes, and Study (PICOS) design, that are presented in Table 1.

Methods

Study Design

This systematic review was conducted in children and adolescents (≤ 19 years old), using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[13] and its respective guidelines[14]. It is also registered prospectively in the International Prospective Register of Systematic Reviews (PROSPERO number: CRD42022313235).

Search Strategy

The search expression was made and used from March to June of 2022, in two databases: *Medline* (*PubMed*®) and *Scopus*®. The search expression was built by one reviewer, while the rest of the team confirmed the process. For *PubMed®*, the following search expression was built: ("food consumption" OR diet* OR (eating[MeSH Terms]) OR ingestion OR food* OR (feeding behavior[MeSH Terms]) OR (meal[MeSH Terms])) AND ((child[MeSH Terms]) OR (adolescent[MeSH Terms])) AND ((child[MeSH Terms]) OR (adolescent[MeSH Terms]) OR pregnan* OR gestational*) AND ("mental well-being" OR "mental health" OR "well-being" OR (quality of life[MeSH Terms]) OR symptom* OR (neurobehavioral manifestations[MeSH Terms]) OR "neurologic dysfunction" OR depression OR anxiety OR stress OR agressive OR emotion*) AND ((dyslexia[MeSH Terms]) OR (Attention Deficit Disorders with Hyperactivity[MeSH Terms]) OR (autism spectrum disorder[MeSH Terms]) OR (Autistic disorder[MeSH Terms]) OR (dyscalculia[MeSH Terms]) OR dyspraxia OR dysphasia OR dysgraphia OR dyslalia OR "special educational needs" OR "special education" OR "TIC disorder" OR "Tourette" OR "trisomy 21" OR "down syndrome" OR "trisomy of the autosomes" OR "cerebral palsy" OR (neurodevelopmental disorders[MeSH Terms]) OR (intellectual

disability[MeSH Terms]) OR "high intellectual potential" OR "learning disabilities" OR "learning disability" OR "communication disorder" OR (motor disorders[MeSH Terms])). Considering *Scopus*® database, a similar search expression was used. Keywords related to SEN were chosen based on terms related to neurodevelopmental disorders found in DSM-V and considering the SEN categories in IDEA program, regarding the distribution of the prevalence of students that received special educational services under this program[3-5].

Eligibility Criteria

The eligibility criteria considered to the studies selection were selected based on PICOS design and are shown in Table 1. For both databases, filters such as language (English and Portuguese) and age (≤ 19 years old) were used. Additionally, for *Medline* (*Pubmed*®), only studies in humans and studies with abstract available were considered.

Table 1. Eligibility criteria of the studies included in this review according to the population, indicator, comparator, outcomes, and study design (PICOS) format.

*Indicator and outcome are different for each specific objective (1 and 2 respectively).

PICOS	Inclusion Criteria	Exclusion Criteria
Population	Children and/or adolescents ≤ 19 years old.	Previously diagnostic of special dietary requirement.
Indicator*	1) Pregnant women's diet or nutrition; 2) Children and/or adolescents' diet or nutrition.	Population ≤ 19 years old or pregnant women previously diagnosed with some special dietary requirement. Diet not related to a special educational need at pediatric age.
Comparator	Not applicable	Not applicable
Outcome*	1) Diagnostic of special educational needs in children and/or adolescents; 2) Symptomatology and/or well-being of children and/or adolescents with special educational needs.	1) A diagnostic of special educational needs in children and/or adolescents not associated, in the article, with pregnant women's diet and/or nutrition; 2) Symptomatology or well-being of children and/or adolescents with special educational needs not associated to children and adolescents' diet;
Study Design	Original studies	Reviews, only abstracts, case studies of one individual, books, paper conferences

Study selection and data extraction

Firstly, two reviewers applied the eligibility criteria and selected the studies for inclusion, by reading the titles and respectively abstracts. Secondly, two reviewers analyzed the full-text studies to decide which ones met the inclusion criteria to enter this systematic review. In case of doubt, when reading the abstracts and the full texts, a third reviewer assisted the decision, based on the support of the literature. The number of studies excluded, and its respective reasons are reported in the PRISMA fluxogram presented in Figure 1.

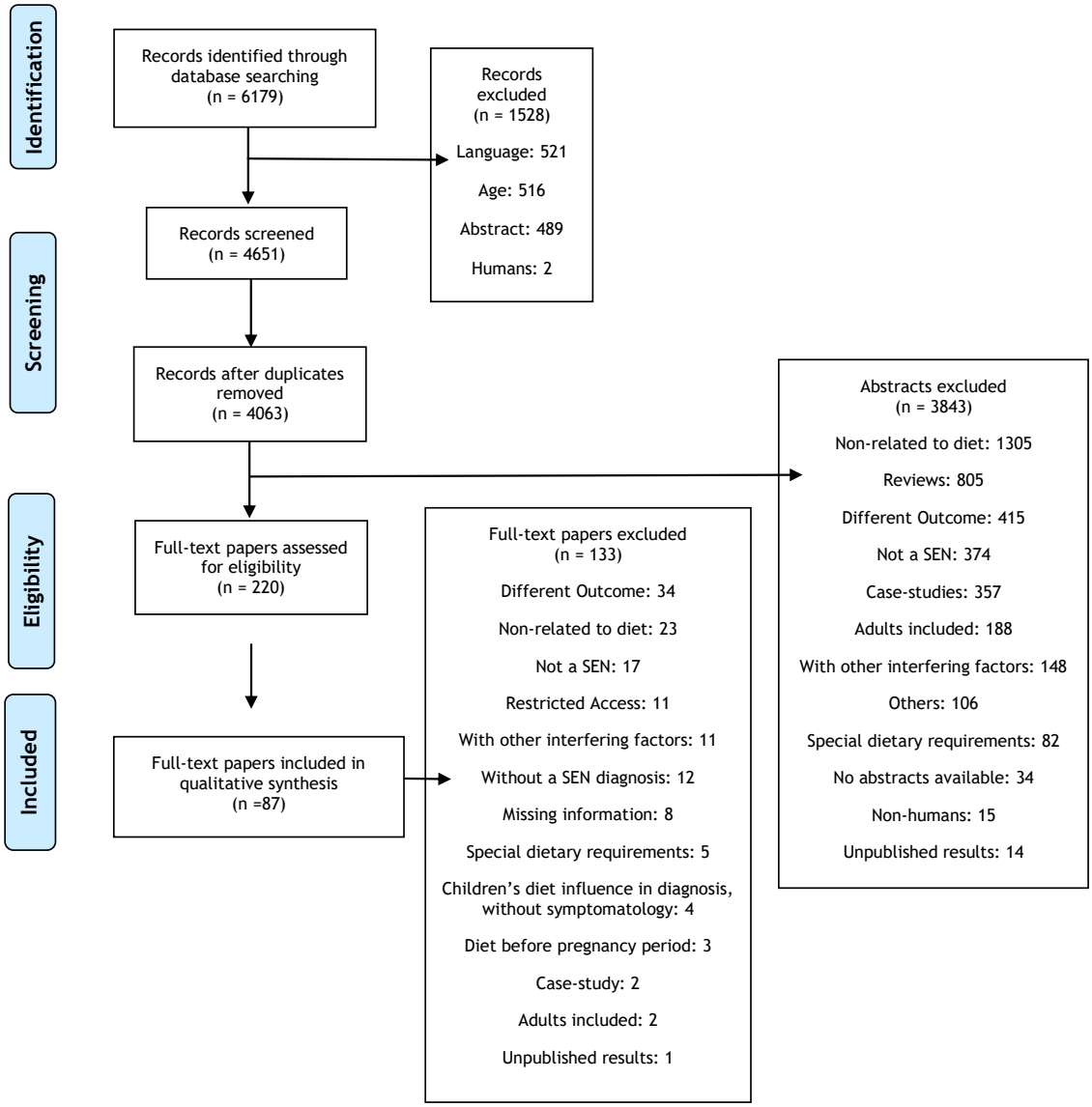

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) fluxogram.

No contact with the authors studies was needed, once all the required data to answer the objectives have already been published.

There was no minimum number of studies considered to include in this review. A study was included if it could answer, at least, one of the two specific objectives. The eligible studies were summarized in Attachment A, according to the name of the SEN studied. This attachment consists in a table that has the following information: type of study, country, children/adolescents' sample size, age and sex, method of diagnosis and/or symptomatology, diet element studied, prevalence of SEN, risk of diagnosis and/or symptomatology/well-being.

Duplicate articles were identified and eliminated using *Endnote*®[15]. Starting from 4063 abstracts screening, this review included 220 studies for eligibility and, of these, 87 were included in the qualitative synthesis (Figure 1).

Results

Regarding the 87 articles included, 13 were cohort studies, 54 experimental studies (40 Randomized Controlled Trial (RCTs), six clinical trials and eight open trials), eight case-control studies and 12 cross-sectional studies. This review included, in total, 544,682 children and adolescents, from birth to 18.7 years old. Of these, 19,541 (3.6%) had a confirmed SEN. Eighty-five studies included children and 51 included adolescents. Forty-six studies were published between 2015 and 2022 and 41 were published between 1975 and 2014. Considering the geographical distribution, 32 studies were conducted in Europe, 23 in America (being 18 in USA), 24 in Asia, seven in Oceania and one in Africa.

Regarding SEN, 41 articles studied **ADHD**, where the SEN prevalence range from 2.2 %[16] to 100 %[17-37], and 34 studied **ASD**, where the SEN prevalence range from 1,3 %[7] to 100 %[38-61]. The remaining SEN included in this review were the following

ones: **learning disabilities**[10, 62-66], **dyslexia**[67, 68], **epilepsy**[69, 70], **Tourette Syndrome (TS)**[71], **Autosomal Trisomy**[72], **pediatric bipolar disorder (PBD)**[73], **intellectual disability**[74], **and Smith-Lemli-Opitz syndrome**[75].

Concerning the different study methods, the most frequently used measurement tools to assess **ADHD diagnosis** were the Diagnostic and Statistical Manual of Mental Disorders, the fourth and fifth edition (DSM-IV and DSM-V) presented in 20/41 articles. For **ADHD symptomatology**, stands out the Conner's Rating Scale and subscales (CRS), used in 14/41 articles, the ADHD Rating Scale (ADHD-RS), used in 10/41 articles, and the Strength and Difficulties Questionnaire (SDQ), used in 6/41 articles). For **ASD diagnosis**, the most frequently used assessment tools were also DSM-IV and DSM-V, presented in 13/34 and 7/34 studies, respectively. Regarding **ASD symptomatology** evaluation, the Childhood Autism Rating Scale (CARS), the Aberrant Behavior Checklist and the Autism Behavior Checklist were the most used ones, presented in eight, six and five of 34 articles, respectively. For the other eight SEN listed, five were already previously diagnosed in the beginning of the study, and considering SEN symptomatology, the scales used were few and very different from each other.

Ten articles have information regarding the association between pregnant women's diet and the diagnosis of SEN in pediatric age, which four were related to ADHD[6, 16, 76, 77], five to ASD[7, 78-81] and one to autosomal trisomy diagnosis[72]. Seventy-eight articles study the association between the diet of children and/or adolescents, with the symptomatology and well-being of children and/or adolescents with ADHD (38 articles), ASD (29 articles), learning disabilities[10, 62-66], dyslexia[67, 68], epilepsy[69, 70], TS[71], PBD[73], intellectual disability[74], and Smith-Lemli -Opitz syndrome[75].

Regarding **pregnant women's diet**, the most studied dietary elements were multivitamin supplementation[7, 72, 78, 80], folic acid supplementation[7, 80, 81], diet quality evaluation[6] and caffeine intake[76, 77].

Considering **ADHD**, one study found that a low diet quality score during pregnancy was associated with an increased risk of an ADHD diagnosis[6]. Two studies did not find any significant relationship between caffeine intake during pregnancy and the incidence of ADHD in children, considering coffee, yerba mate, tea, or cola[76, 77].

Regarding **ASD**, two studies found a negative association between multivitamin supplementation during pregnancy and the risk of ASD diagnostic[7, 80], while one study found a positive association considering only high and low doses[78]. In one of these studies, when folic acid or iron supplementation were added to the multivitamin treatment, no significant changes were observed[80]. However, another study found a protective effect of folic acid supplementation during pregnancy, considering ASD diagnostic[7].

Considering **children and adolescent's diet**, the most studied dietary elements were polyunsaturated fatty acids (PUFA) supplementation in 17 articles, gluten/casein-free diet in 13 articles, vitamin D supplementation[21, 38, 49-51, 82, 83], micronutrient supplementation[19, 36, 62, 65, 73], breastfeeding[74, 84-86], magnesium[21], and folic acid[59] supplementation.

Considering **ADHD**, PUFA supplementation is associated to symptomatology improvements in six studies, including ADHD symptoms[17, 22, 30, 87], memory function[33] and word reading improvement[88]. However, in four studies, none of those associations were found[20, 33, 34, 89]. Five studies found associations between the intake of processed food and food with high-fat, sugar, and salt (fast-food, instant noodles, sugar-sweetened beverages, fried food, sweet deserts, and high

energy intake) and higher symptomatology manifestation[8-10, 90, 91]. Finally, two studies found a protective association between breastfeeding and ADHD symptoms[84, 85], while one study did not found any association[86].

Regarding **ASD**, three studies found an association between vitamin D3 supplementation and ASD symptoms improvement[49, 50, 83]. However, two studies did not find such associations[38, 49]. PUFA supplementation was associated with symptoms improvement in three studies[50, 51, 54], even though there was no association in one study[61]. In one of these studies, combined vitamin D3 and PUFA supplementation showed a protective effect on symptomatology[51]. Gluten and casein-free diets showed a significant effect on improving gastrointestinal and behavioral symptoms in four studies[44, 55-57], although this relationship was not found to be significant in other eight articles[39-41, 43, 45, 47, 56, 92].

Considering **epilepsy**, two studies showed significant improvements considering the disease severity, including seizure reduction, during a ketogenic diet treatment[69, 70]. For **intellectual disabilities**, breastfeeding was associated with symptomatology improvement in one study[74]. In **dyslexia**, PUFA supplementation had a protective association with symptomatology in one study[67], while another did not find any association[68]. Regarding **learning disabilities**, significant improvements in cognitive function, for multivitamin and PUFA supplementation were found in three[62, 65, 66] and one study[64] , respectively.

Discussion

In this systematic review, the following SEN were considered according to the definition of each study included: ADHD, ASD, learning disabilities, dyslexia, epilepsy, TS, Autosomal Trisomy, PBD, intellectual disability and Smith-Lemli - Opitz syndrome. To analyze the results of this review, it needs to be taken into

consideration that a SEN can include a wide range of different disabilities and spectrums, being sometimes difficult to isolate each one from another. For example, in this review, a child was identified having both ADHD and learning disabilities, belonging to the "multiple disabilities" category of the IDEA program[3, 10].

In general, the studies included in this review are widely distributed across the different continents of the world, corroborating that this theme is a global theme studied around the world, that has gained importance over the years[12].

Regarding the diagnostic methods used in the different articles included in this review, the main tool found was the DSM (mainly 4th and 5th Edition), appearing in 44 out of 87 articles. Apart from the DSM, other additional 20 methods for diagnostic and 66 methods for symptomatology were found in the different studies, in total. This fact helps to explain some differences in these review results. For example, there are studies related to the use of gluten-free and/or casein-free diet in ASD included in this review that, statistically, do not show any significant improvement of the disorder, but an improvement in the outcome was reported by parents [43, 47]. Additionally, for the same dietary element studied in this review, the symptomatology type studied was very diverse for the same SEN, making the reliability of results and comparison between studies difficult. For example, regarding the association between PUFA supplementation and ADHD symptomatology in children and adolescents, one article studies ADHD general symptoms with Child Behavior Checklist (CBCL) and Strengths and Weaknesses of ADHD symptoms and Normal Behavior Scale (SWAN)[17], while other article studies only hyperactivity symptoms with Conners' Abbreviated Symptom Questionnaires (ASQ-P)[22].

Considering the relationship between **pregnant women's diet and SEN diagnostic** in this review, it does not seem to exist any association between **caffeine consumption** and the risk of **ADHD** in childhood[76, 77]. In a previously review published in 2015 assessing this subject, also no association was found[93]. Therefore, it doesn't seem to exist supporting evidence to restrict caffeine consumption to pregnant women when it comes to ADHD, but further research should be conducted to reach more consistent results.

Considering a previously meta-analysis, **pregnant folic acid or multivitamin supplementation** showed to be protective against children's risk of **ASD** (Relative Risk (RR) = 0.64, 95% CI = 0.46, 0.90)[94], which is consistent with the results obtained in this present review. It needs to be taken into consideration that the only one study included in this review showing damaging effects of pregnant multivitamin supplementation in ASD risk in offspring, referred only to high (>5 times/week) and low (≤2 times/week) doses, supporting that moderate supplementation should be recommended[78].

Regarding the relationship between **children and adolescent's diet and SEN symptomatology**, according to a critical review made in 2020, there are many inconsistent results about the effect of **PUFA** supplementation on ADHD in children and adolescents, concluding that further research is necessary [95]. In the present review, 6 out of 10 studies showed a protective effect[17, 22, 30, 33, 34, 87], also showing this inconsistency.

Considering different foods and beverages, our results include 5 studies that found an association between the intake of **processed food and beverages with high-sugar, high-fat, and salt** content with the increase of ADHD severity[8-10, 90, 91], while **fruits, vegetables and milk products** are associated with symptomatology

improvement[8, 10]. Indeed, it has been already showed an association between sugar and sugar sweetened beverages intake and ADHD symptoms in a 2020 meta-analysis, which corroborate these results[96]. In another meta-analysis published in 2020, not only "junk food" and/or a "Western" dietary pattern increased the odds of ADHD in children, but also a "healthy" dietary pattern highly loaded with **vegetables and fruits** decreased these odds[97], which is in agreement with the results found in this present systematic review. Although these meta-analysis findings, more research regarding dietary patterns in only ADHD children and adolescents should be made, considering that the referred previously studies include both ADHD and non-ADHD children.

Considering **breastfeeding**, two meta-analyses conclude that it seems to be associated with a lower risk of ADHD in children[98, 99]. These findings seem to be in agreement with our results, once it included two in three studies that found a protective association between breastfeeding and the severity of symptoms in children with ADHD[84-86]. Further studies that distinguish the risk of ADHD diagnostic vs. the severity of symptoms of children with an established diagnostic, regarding their association with breastfeeding, should be conducted.

Regarding **ASD** symptoms and their association with **vitamin D supplementation**, some inconsistent results were found in this review. Compared to the existing evidence in the literature, although that there are also some conflicting results, overall vitamin D supplementation seems to be beneficial in improving symptomatology in a previously systematic review[100]. Some reasons for the conflicting results can involve the different dosage levels considered in the studies included and the different proportion of individuals with vitamin D deficiency,

considering that autistic children tend to have a higher risk of vitamin D deficiency, which can influence the results[100, 101].

Regarding the effect of **PUFA supplementation** on ASD symptoms, overall, it seems to be an association between the two factors, with only one in five studies included showing no association[61]. In a previously meta-analysis, there are some inconsistent results described, and a lack of studies focusing on this topic[102]. For this reason, further research is recommended.

Considering **gluten-free and/or casein-free diet**, nine out of 13 studies included in this review did not support the use of this diet as a treatment to **ASD severity**[39-41, 43, 45-47, 56, 92]. Interestingly, even though the statistically insignificant results, parents tend to report an improvement in ASD symptoms of their children[43, 47]. A systematic review published in 2018 support our results, showing no evidence for the use of these diets in ASD, regarding the improvement of symptoms' severity. This study also referred that some differences found in their studies results were also related to the use of parent-report tools[103].

Considering the relationship of children and adolescent's diet and **epilepsy**, the two studies included support the protective effect of **ketogenic diet** in seizure reduction[69, 70]. These results are supported by the existing evidence presented in the literature[104].

Lastly, relatively to the studies included in this review about **learning disabilities**, it has been found an association between its symptom's improvement and **multivitamin supplementation**[62, 65, 66]. Although that there are no systematic reviews addressing this specific subject, a review published in 2012 suggested cognitive and behavioral benefits after vitamin and mineral supplements with or without n-3 PUFA supplementation[105].

Regarding the **other SEN studies included** in this review (dyslexia, TS, Autosomal Trisomy, PBD, intellectual disability, and Smith-Lemli-Opitz syndrome), due to the small number of studies included of each SEN and considering, at the same time, the different dietary elements, it is not possible to extrapolate results and discuss them. For this reason, further studies about these SEN should be conducted.

This systematic review presents some limitations. Firstly, quality assessment of each article was not conducted, which has an influence in the discussion of the presented results. The sample size of each study included is widely variable, as well as the different methods used in each study to assess the diagnostic and/or the symptomatology of one same disorder (for example, different scales and report methods). These different methodologies makes it difficult to compare and discuss results.

Apart from these limitations, there are strengths associated to this systematic review. This review is the first one to assess the different disabilities that are eligible for a SEN classification, and to study the influence of diet in pregnant, and child/adolescents with the diagnosis and symptomatology of SEN, respectively. This review included 87 articles, with a high proportion of experimental studies, including RCTs, allowing the establishment of causes and effects, which is essential to respond to the concrete objectives of this review. The present study can contribute to the field of pediatric clinical nutrition by helping to establish guidelines for pregnant women and children and adolescents with SEN.

Conclusions

In this systematic review, it was included studies referring to the follow SEN: attention-deficit/hyperactivity disorder, autism spectrum disorder, learning disabilities, dyslexia, epilepsy, Tourette syndrome, autosomal trisomy, pediatric bipolar disorder, intellectual disability, and Smith-Lemli-Opitz syndrome.

Regarding the effect of the pregnant women's diet, it stands out the fact that does not seem to exist an association between caffeine consumption from diet and the risk of ADHD in children and adolescents. A protective effect stands out, considering pregnant multivitamin supplementation in the risk of ASD diagnostic.

Regarding the effect of diet of children and adolescents with SEN, it stands out the fact that the consumption of fast-food and sugar-sweetened beverages are associated with an increase of ADHD symptom's severity.

In addition, it was not found an association between gluten-free and/or casein-free diet and ASD symptomatology. Maternal breastfeeding seems to have a protective effect in ASD symptoms. Vitamin D and PUFA supplementation presented inconsistent results, regarding their effect on ASD symptomatology.

In addition, more studies are needed to support the results of this review, regarding the association of each dietary element studied in pregnant women/children/adolescents, and the respective association with their diagnosis and symptomatology. Until then, the results of this review are extremely relevant to help the development of guidelines for dietary recommendations for this target population.

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Attachment A – Characteristics of the studies included, related to the Influence of diet in children and adolescents with SEN.

Legend: ADD: Attention-deficit disorder | ADHD: Attention-deficit/hyperactivity disorder | CI: Confidence Interval | DSM: Diagnostic and Statistical Manual of Mental Disorders | HR: Hazard Ratio | ICD-10: International Classification of Diseases, 10th Revision | OR: Odds Ratio | RCT: Randomized Controlled Trial | RR: Relative Risk | SEN: Special educational need

SEN	*Author, year (reference)*	*Type of study*	*Country*	*Child/ adolescent Sample size, age, and sex*	*Method for diagnostic/ symptomatology assessment*	*Diet element study (in pregnancy or during pediatric age)*	*Prevalence of SEN*	*Risk of diagnostic*	*Symptomatology/ Well-being*
ADHD	Abel, M. H. et al., 2017[16]	Cohort study (8 years follow-up)	Norway	n = 77164 | 0-8 years | 48.8 % female	Diagnostic: previously obtained	IN PREGNANCY: iodine intake from food vs supplementation based on the Food Frequency Questionnaire	n = 1725 (2.2 %)	Non-users of supplemental iodine (n = 53360): no association between iodine intake from food and risk of child diagnostic (p = 0.89); Iodine supplementation (≥ 160 µg/day) in 0 - 12 gestational weeks associated with an increased risk of child diagnostic (HR = 1.50, 95 % CIs = 1.07-2.10)	---
ADHD	Bélanger, S. A. et al., 2009[17]	RCT (16 weeks)	Canada	n = 26 | 6.9-11.9 years | 30.8 % female	Diagnostic: DSM-IV[ii] | Symptomatology: Strengths and Weaknesses in ADHD and Normal Behaviors (SWAN); Conners' rating scales	IN PEDIATRIC AGE: intervention group (A): n-3 polyunsaturated fatty acid (PUFA) supplementation (20-25 mg/kg/day of EPA + 8.5 - 10.5 mg/kg/day of DHA) for 16 weeks; Placebo group (B): placebo for 8 weeks (phase 1) + n-3 (PUFA) supplementation for 8 weeks (phase 2)	n = 37 (100 %)	---	For both groups (A - n = 13 and B - n = 13), there was a significant decrease of ADHD symptoms (Conners' subscales of Cognitive problems/inattention, Hyperactivity and ADHD index), between baseline and the end of phase 2 (p < 0.05).
ADHD	Barling, J. et al., 1985[106]	Case-control study	South Africa	n=27 | 9.15 years (mean)| no information about gender	Diagnostic: Teacher Rating Scale (TRS) | Symptomatology: Behavior Problem Checklist	IN PEDIATRIC AGE: sucrose consumption by the 7-day dietary record reply by the mother	n = 13 (48 %)	---	No significant relationships emerged between sucrose consumption and hyperactivity or aggression symptoms (p > 0.05).
ADHD	Arnold, L. E. et al., 2005[18]	Cross-sectional study	USA	n = 48 | 5-10 years | 22,9 % female	Diagnostic: DSM-IV |Symptomatology: Conner's Rating Scales—Revised (severity)	IN PEDIATRIC AGE: serum zinc levels were determined regarding the Food Frequency Questionnaire report by parents	n = 48 (100 %)	---	Lower zinc levels associated with more ADHD inattention symptoms (p = 0,002); Zinc levels were not significantly associated with hyperactive-impulsive symptoms (p = 0,35).

Attachment A (continued)

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ADHD	Barry, R. J. et al., 2012[107]	RCT (1 week)	Australia	n = 36 | 8-13 years | 27,8 % female	Diagnostic: DSM-IV | Symptomatology: Conner's Rating Scales—Revised (severity)	IN PEDIATRIC AGE: Caffeine levels by administration of two identical gelatin capsules, containing either 80 mg/capsule of caffeine or placebo in 2 sessions	n = 18 (50 %)	---	Increase in caffeine-induced arousal in the ADHD group were positively associated with their hyperactivity/impulsivity levels (r = 0.41, *p* = 0.044, partial 2 = 0.171).
ADHD	Borge, T. C. et al., 2021[6]	Cohort study (8 years follow-up)	Norway	n = 77768 | 0-8 years | 48,9% female	Diagnostic: previously obtained according to ICD-10 | Symptomatology: Parent Rating Scale for Disruptive Behavior Disorders (severity)	IN PREGNANCY: diet quality during pregnancy reported on the food frequency questionnaire (FFQ) and assessed with Prenatal Diet Quality Index (PDQI) and Ultra-Processed Food Index (UPFI); IN PEDIATRIC AGE: diet assessed by parent-reported food intake questions and evaluated using Diet Quality Index (DQI)	n = 2255 (2.9 %)	A 1 Standard Deviation increase in PDQI score was associated with a 13 % decrease of the risk of ADHD diagnostic (RR = 0.87, CI: 0.79, 0.97).	Child diet (DQI) was not associated to ADHD symptoms score at 8 years (*p* > 0.05).
ADHD	Borlase, N. et al., 2020[19]	RCT (10 weeks)	New Zealand	n = 27 | 8.1-13.2 years | 0 % female	Diagnostic: DSM-V and Kiddie Schedule for Affective Disorders and Schizophrenia Lifetime Version (K-SADS-PL) | Symptomatology: Clinical Global Impressions Improvement (CGI-I) scale; Children's Global Assessment Scale (CGAS); ADHD Rating Scale IV (ADHD-RS-IV); Conners Parents and Teacher Rating Scale (CPRS and CTRS);	IN PEDIATRIC AGE: micronutrients supplementation (Daily Essential Nutrients (DEN)) or placebo	n = 27 (100 %)	---	The micronutrient group showed a significant clinical benefit on the CGI-I global score (ADHD measure of symptoms) (*p* = 0.01) compared to placebo group.

Attachment A (continued)

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SEN	*Author, year (reference)*	*Type of study*	*Country*	*Child/ adolescent Sample size, age, and sex*	*Method for diagnostic/ symptomatology assessment*	*Diet element study (in pregnancy or during pediatric age)*	*Prevalence of SEN*	*Risk of diagnostic*	*Symptomatology/ Well-being*
ADHD	Bos, D. J. et al., 2015[87]	RCT (16 weeks)	The Nether-lands	n = 79 | 8-15 years | 0 % female	Diagnostic: DSM-IV; Diagnostic Interview Schedule for Children-Parent Version (DISC-P) | Symptomatology: Child Behavior Checklist (CBCL); Strengths and Weaknesses of ADHD symptoms and Normal behavior scale (SWAN)	IN PEDIATRIC AGE: 10g of omega-3 (either normal or fortified with margarine) supplementation containing 650 mg DHA and 650 mg EPA, or placebo	n = 40 (50,6 %)	---	After supplementation with omega-3 PUFAs, ADHD investigation group had significantly reduced scores on CBCL attention problems, compared to placebo group ($p < 0.001$).
ADHD	Crippa, A. et al., 2019[20]	RCT (6 months)	Italy	n = 50 | 7-14 years | 8 % female	Diagnostic: DSM-IV; Development and Well-Being Assessment (DAWBA) | Symptomatology: ADHD Rating Scale (ADHD-RS); Conners' Parent Rating Scale-Revised (CPRS-R); Clinical Global Impression-Improvement and Severity scale (CGI-I and CGI-S)	IN PEDIATRIC AGE: An Active supplement, namely 2 soft gelatin pearls per day providing a dose of 500 mg algal DHA or a placebo	n = 50 (100 %)	---	There were no significant differences on ADHD rating scale (primary outcome) in DHA group, compared to placebo group ($p > 0.05$), indicating no significant benefit of supplementation.
ADHD	Del-Ponte, B. et al., 2016[76]	Cohort study (11 years follow-up)	Brazil	n = 3485 | 0-11 years | 48.1 % female	Diagnostic: Development and Well-Being Assessment (DAWBA)	IN PREGNANCY: caffeine intake from coffee and yerba mate evaluated with a daily frequency questionnaire	n = 143 (4.1 %)	There was no association between maternal caffeine consumption and incidence of ADHD at 11 years in children, during the three pregnancy trimesters and the entire pregnancy ($p>0.05$).	---
ADHD	Hemamy, M. et al., 2021[21]	RCT (8 weeks)	Iran	n = 66 | 9.11 ± 1.61 years | 30.3 % female	Diagnostic: DSM IV | Symptomatology: Strength and difficulties questionnaire (SDQ) (mental health status)	IN PEDIATRIC AGE: vitamin D (50,000 IU/week) plus magnesium (6 mg/kg/day) supplementation or placebo	n = 66 (100 %)	---	Children receiving vitamin D plus magnesium (n = 33) showed a significant reduction in emotional problems, conduct problems, peer problems, prosocial score, total difficulties, externalizing score, and internalizing score ($p < 0.05$) of SDQ, compared with children treated with the placebo (n = 33).

Attachment A (continued)

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ADHD	Hariri, M. et al., 2012[22]	RCT (8 weeks)	Iran	n = 103 | 6 -12 years| 35 % female	Diagnostic: Conners' Abbreviated Questionnaires (ASQ-P) scores for hyperactivity greater than 14 | Symptomatology: ASQ-P	IN PEDIATRIC AGE: supplementation with a total daily dose of 900mg n-3 fatty acids (635mg EPA, 165mg DHA and 100mg other n-3 fatty acids) or placebo	n = 103 (100 %)	---	A significant improvement was observed in hyperactive behaviors rated ASQ-P scores in the n-3 group (p<0.01) comparing to placebo group after 8-weeks intervention, compared to baseline.
ADHD	Julvez, J. et al., 2007[84]	Cohort study (4 years follow-up)	Spain	n = 500 | 0 - 4 years | 49.8 % female	Diagnostic: DSM-IV | Symptomatology: McCarthy Scales of Children's Abilities (MCSA) (cognitive and motor capabilities); ADHD-DSM-IV; Social Competence (CPSCS)	IN PEDITRIC AGE: duration of breastfeeding, assessed through Interviewer-administered questionnaires	No information about the diagnostic prevalence only about symptoma-tology.	---	Long-term breast-feeding (> 28 weeks, n = 98) was associated with less attention-deficit hyperactivity symptom scores (RR = 0.56; CI: 0.37 – 0.85, after > 12 weeks) (p < 0.05), compared to the group that was breastfed less than 2 weeks (n = 101)
ADHD	Hirayama, S. et al., 2014[23]	RCT (2 months)	Japan	n = 36 | 4–14 years | 5.6 % female	Diagnostic: previously obtained | Symptomatology: DSM-IV-TR; (severity); Wechsler Intelligence Scale for Children (WISC-III) (memory); GO/NO-GO task (mental performance)	IN PEDIATRIC AGE: placebo or supplementation with cocoa flavored chews containing 100 mg of soy-derived phosphatidylserine (PS) per chewable (2 chews per day)	n = 36 (100 %)	---	PS supplementation (n = 19) resulted in significant improvements in: ADHD (p < 0.01); short-term auditory memory (p < 0.05) and inattention and impulsivity (p < 0.05), between baseline and after intervention, compared to placebo group (n = 17).
ADHD	Hontelez, S. et al., 2021[24]	RCT (8 weeks)	The Nether-lands	n = 79 | 8 - 10 years | 0 % female	Diagnostic: DSM-IV criteria | Symptomatology: ADHD Rating Scale (ARS)	IN PEDIATRIC AGE: Free-food diet (FFD) during 32-33 days of rice, turkey, vegetables, pears, olive oil, ghee, salt, rice drink with added calcium and water. During the first 2 weeks, this diet was extended with some other foods, allowing lamb, butter and small portions of wheat, corn, potatoes, some fruits, and honey.	n = 79 (100 %)	---	At the end of the FFD period, the mean of ARS score was significantly lower than the mean before the FFD period, indicating a significant improvement of symptoms (p < 0.0001).

Attachment A (continued)

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SEN	*Author, year (reference)*	*Type of study*	*Country*	*Child/ adolescent Sample size, age, and sex*	*Method for diagnostic/ symptomatology assessment*	*Diet element study (in pregnancy or during pediatric age)*	*Prevalence of SEN*	*Risk of diagnostic*	*Symptomatology/ Well-being*
ADHD	Hsu, C. D. et al., 2021[25]	RCT (8 weeks)	Taiwan	n = 20 | 10.0 ± 2.1 years | 15 % female	Diagnostic: DSM-IV-TR | Symptomatology: Swanson, Nolan, and Pelham (SNAP-IV) questionnaire	IN PEDIATRIC AGE: placebo: maltodextrin (75%) and magnesium stearate (25%) Supplement: 1 capsule (if BW) < 50 kg) or 2 (if BW > 50 kg) of pine bark extract (PE)/day containing/capsule: 25 mg (Oligopin®) for 4 weeks + 2 weeks of washout + 4 weeks of placebo or PE	n = 20 (100 %)	---	PE supplementation caused a significant reduction in the SNAP-IV inattention items and in teacher's hyperactivity-impulsivity item (p < 0.05) compared to baseline.
ADHD	Hirayama, S. et al., 2004[89]	RCT (2 months)	Japan	n = 40 | 6.8-11.3 years (mean age = 9 years) | 20 % female	Diagnostic: DSM-IV | Symptomatology: DSM-IV; Development Test of Visual Perception; Questions to evaluate aggression and impulsivity	IN PEDIATRIC AGE: placebo or DHA supplementation (fermented soybean milk with 600 mg DHA/125 ml, 3x a week, bread rolls with 300 mg DHA/45 g, 2x a week and steamed bread with 600 mg DHA/60 g, 2x a week)	n = 31 (80 %)	---	Considering children with ADHD, visual short-term memory, and errors of commission (continuous performance) significantly improved in the control group (n = 16) compared with the changes over time in the DHA group (n = 16) (p < 0.05). DHA supplementation did not improve ADHD-related symptoms.
ADHD	Joshi, K. et al., 2006[108]	Clinical trial (pilot study) (3 months)	India	n = 60 | 7.5 years (control) and 8.0 years (ADHD group) | 26.7 % female	Diagnostic: DSM-IV | Symptoms: Parent Rating Scale	IN PEDITRIC AGE: flax oil supplementation (200 mg ALA content + 25 mg Vitamin C twice a day)	n = 30 (50 %)	---	In ADHD group (n = 30), there was a highly significant decrease in individual scores for total hyperactivity, self-control, psychosomatic, restlessness, inattention and impulsivity (p < 0.001) and a significant decrease in scores of social and learning problems (p < 0.05) in post-supplementation period, compared to pre-supplementation period.

Attachment A (continued)

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ADHD	Cremonte, M et al., 2017[26]	Clinical trial (pilot study) (6 months)	Italy	n = 30 | 6-15 years | 7 % female	Diagnostic: DSM-IV | Symptomatology: Child Global Assessment Scale (C-GAS); Swanson, Nolan, and Pelham (SNAP-IV) questionnaire; Conners' parent rating scale (CPRS); Bell's Test and Tower of London test (executive functioning); Wechsler Intelligence Scale for Children III (WISC-III scale)	IN PEDIATRIC AGE: Klamin® (Phenylethylamine (PEA), naturally contained in the Klamath Lake microalgae) supplementation	n = 30 (100 %)	---	After 6 months of therapy for all patients, there was a significant improvement of their overall functioning, behavioral aspects related to inattention and hyperactivity–impulsivity, attention functions in both the selective and sustained component and executive functions (C-GAS score, SNAP-IV inattention, hyperactivity and total score, London Tower Test and Bell's Test) ($p < 0.005$).
ADHD	Dölp, A. et al., 2020[27]	Uncontrolled open-label dietary intervention study (22 weeks)	Germany	n = 10 | 8 - 14 years | 20 % female	Diagnostic: ICD-10 | Symptomatology: ADHD Rating Scale IV (ARS); Childhood Behavior Checklist (CBCL); Abbreviated Connor´s rating scale (ACS); DISYPS-II FBB-ADHD .	IN PEDIATRIC AGE: Phase T0-T1 (2 weeks): regular diet; Phase T1-T2 (4 weeks): diet only with limited selection of hypoallergenic foods; Reintroduction Phase T2-T4: different food groups were successively tested (16 weeks)	n = 10 (100 %)	---	There was a significant mean improvement for the ARS scores and for DISYPS-II FBB-ADHD scale, in every subscale, and for CBCL in "Externalizing", "Internalizing", "Withdrawn", "Anxious/depressed", "Delinquent behavior" and "Aggressive behavior" after diet (T2 vs. T1) ($p \leq 0.036$).
ADHD	Kim, K. M. et al., 2018[8]	Cross-sectional study	Korea	n = 16831 | 9.29 years ± 1.71 | 50.2% female	Symptomatology: ADHD Rating Scale (ARS)	IN PEDIATRIC AGE: evaluation of dietary habits assessed with a parent-reported food frequency questionnaire (to have data regarding fast food, soft drinks, instant noodles, fruit and vegetables and milk)	No information about the diagnostic prevalence only about symptoma-tology.	---	Children who consumed fast food, instant noodles and soft drinks more frequently had higher K-ARS scores and higher odds ratios for ADHD risk than the children who never consumed these foods ($p < 0.05$). Children who consumed fruit and vegetables more frequently had significantly lower K-ARS scores and lower odds ratios for ADHD risk than those children who consumed these foods less frequently ($p < 0.05$).

Attachment A (continued)

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ADHD	Ng, K. H. et al., 2009[28]	Cross-sectional study	Australia	n = 79 | 9.3 ± 1.7 years | 27.8 % female	Diagnostic: Conners' Parent Rating Scales (CPRS) scores > 90th percentile | Symptomatology: CPRS - ADHD Index	IN PEDIATRIC AGE: evaluation of diet with a weighted food record during 3 non-consecutive days to assess PUFA intake	n = 79 (100 %)	---	There were no significant correlations found between PUFA intake and ADHD symptoms (p > 0.05). Likewise, no significant correlations were found between amount of fish/seafood and meat/egg consumption and ADHD symptoms (p > 0.05).
ADHD	Raz, R. et al., 2009[29]	RCT (7 weeks)	Israel	n = 63 | 7-13 years | no information about gender	Diagnostic: previously obtained | Symptomatology: Conners' Rating Scale; Continuous Performance Test	IN PEDIATRIC AGE: supplement contained 480 mg of linoleic acid and 120 mg of a-linolenic acid, and the placebo contained 1000 mg of vitamin C	n = 63 (100 %)	---	No significant differences in ADHD symptoms were found between the 2 groups after the treatment (p > 0.05)
ADHD	Lien, L. et al., 2006[90]	Cross-sectional study	Norway	n = 5498 | 15-16 years | 49,4 % female	Diagnostic: Strengths and Difficulties Questionnaire (SDQ) - Hyperactivity sub score > 90th percentile | Symptomatology: SDQ - Hyperactivity	IN PEDIATRIC AGE: the following question was asked "How much do you normally drink cola or 'fizzy' drinks with sugar?"	n = 508 (9,1 %)	---	For boys, drinking 1 or more glass a day of soft drinks (n = 1221) was associated with more hyperactivity symptoms compared to drinking no soda at all. (example: > 4 glasses/d: OR = 4.15, 95% CI: 2.80, 6.16))
ADHD	Yu, C.J. et al., 2016[9]	Case-control study	Taiwan	n = 332 | 4-15 years | 28.1 % female	Diagnostic: DSM-IV | Symptomatology: Swanson, Nolan and Pelham (SNAP-IV) questionnaire; SNAP-IV Teacher and Parent Rating Scale	IN PEDIATRIC AGE: sugar sweetened beverages consumption and dietary habits evaluated with a questionnaire administered by a trained interviewer to the caretaker	n = 173 (52.1%)	---	Children who consumed 1-6 servings of SSBs/week and children who consumed 7 or more servings of SSBs/week (n = 82) had a higher risk of having ADHD symptoms, compared with those who did not consume SSBs (n = 19) (OR = 1.36, CI95%: 0.61, 3.05 for 1-6 servings; OR = 3.69, CI 95%: 1.291, 10.60 for 7 or more servings)

Attachment A (continued)

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ADHD	Iv, N. et al., 2022[109]	Cohort study (5 years follow-up)	France	n = 1432 | 2-8 years | 47.9 % female	Symptomatology: Strengths and Difficulties Questionnaire (SDQ) - (Hyperactivity and Inattention)	IN PEDIATRIC AGE: dietary intake at the age of 2 years collected using a Food Frequency Questionnaire (FFQ) - 3 dietary patterns were identified: processed and fast foods; labeled guidelines; baby foods.	No information about the diagnostic prevalence only about symptoma-tology.	---	The score on the labeled guidelines dietary pattern was negatively associated with the risk of having hyperactivity-inattention symptoms (OR: 0.75; 95% CI: 0.60–0.94), contrary to adherence to the baby foods dietary pattern (OR: 1.41; 95% CI: 1.16–1.71).
ADHD	Loomans, E. M. et al., 2012[77]	Cohort study (6 years follow-up)	The Netherlan ds	n = 3439 | 0-6 years | 50.2 % female	Diagnostic: Strengths and Difficulties Questionnaire (SDQ) with a score > 17th percentile | Symptomatology: SDQ	IN PREGNANCY: dietary caffeine (tea, cola, coffee) intake evaluated with a questionnaire at the 16th week of gestation	n = 257 (7,5 %)	Caffeine intake was not associated with a higher risk for behavior problems or with suboptimal prosocial behavior (p > 0.05).	---
ADHD	Milte, C. M. et al., 2012[88]	RCT (4 months)	Australia	n = 87 | 7-12 years | 20,7 % female	Diagnostic: medical diagnostic or Conners Parent Rating Scale (CPRS) > 90th percentile | Symptomatology: Wechsler Individual Achievement Test III (literacy); Wechsler Scale of Children's Intelligence III (vocabulary)	IN PEDIATRIC AGE: supplementation with 500 mg fish-oil capsules per day containing 1109 mg of EPA and 108 mg of DHA (EPA–rich oil); a fish-oil providing 264 mg EPA and 1032 mg DHA (DHA–rich oil), or a safflower oil (control) providing 1467 mg/d of u-6 PUFA linoleic acid (LA)	n = 87 (100 %)	---	There were no significant differences between the supplemented groups (n = 30; n = 28) in relation to the control group (n = 29), concerning ADHD index (p > 0,05). An increased proportion of DHA was associated with improved word reading (r = 0.394).
ADHD	Perera, H. et al., 2012[30]	RCT (6 months)	Sri Lanka	n = 94 | 6-12 years | 27 % female	Diagnostic: DSM-IV | Symptomatology: checklist to parents and teachers' application	IN PEDIATRIC AGE: intervention group supplemented with a combined omega3 and omega6 preparation or control group supplemented with placebo	n = 94 (100 %)	---	After 6 months, the intervention group (n = 48) had a significant improvement in all symptoms evaluated (p < 0.05), except for distractibility (p = 0.55), compared to placebo group (n = 46).

Attachment A (continued)

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ADHD	Pelsser, L. M. et al., 2010[31]	RCT (7 weeks)	The Nether-lands	n = 24 | 3-8 years | 20.8 % female	Diagnostic: DSM-IV | Symptomatology: Physical Complaints Questionnaire (behavior, physical and sleep complaints)	IN PEDIATRIC AGE: a 2-week baseline diet (normal diet), followed by an elimination diet for 5 weeks (few foods diet consisting of a limited number of hypoallergenic foods, like rice, turkey, lamb, a range of vegetables, pears, and water). Diet assessed with an extended diary filled by parents	n = 24 (100%)	---	After intervention, there was a significantly decrease of the total number of complaints, including sleep complaints (p = 0.001) in the diet group (n = 13), compared to control group (n = 11).
ADHD	Pelsser, L. M. et al., 2011[32]	RCT (13 weeks)	The Nether-lands	N = 100 | 4 - 8 years | 14 % female	Diagnostic: Structured Psychiatric Interview (SPI) | Symptomatology: ADHD rating scale (ARS); Abbreviated Conners' Scale (ACS); Strengths and Difficulties Questionnaire (SDQ).	IN PEDIATRIC AGE: 5 weeks of a restricted elimination diet (diet group) or a healthy diet (control group. Then, those with an improvement of at least 40% on the ADHD rating scale [ARS] from the diet group proceeded with a 4-week, added to the diet high-IgG or low-IgG foods.	n = 100 (100 %)	---	Between baseline and the first phase, those who were in diet group (n = 50) had significantly less ARS and ACS scores than those who were in control group (n = 50) (p < 0.0001). At the second phase, reintroducing foods led to a significant behavioral relapse in 63.3 % of the clinical responders (p < 0.001).
ADHD	Widenhorn-Müller, K. et al., 2014[33]	RCT (16 weeks)	Germany	n = 95 | 8.91 ± 1.35 years | 22.1 % female	Diagnostic: DSM-IV | Symptomatology: FBB ADHS parent-rated and teacher-rated questionnaires (DISYPS-II); Child Behavior Checklist (CBCL); Teacher's Report Form (TRF) (academic performance, social problems, depression, anxiety, and aggressive behavior)	IN PEDIATRIC AGE: intervention group: two soft gelatin capsules with a daily dose of 720 mg omega-3 fatty acids (600 mg EPA, 120 mg DHA) and 15 mg of vitamin E | placebo group: two olive oil-containing capsules per day	n = 95 (100 %)	---	At the end of intervention, there were no significant differences in scores of DISYPS-II questionnaire, CBCL scores and TRF, between both groups (p > 0.05). However, there was a significant improvement in working memory function (index score) in the intervention group (n = 46) after 16 weeks, comparing to placebo (n = 49).

Attachment A (continued)

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ADHD	Stevens, L. et al., 2003[34]	RCT (4 months)	USA	n = 47 | 6 – 13 years | 11 % female	Diagnostic: previously obtained | Symptomatology: Conners' Abbreviated Symptom Questionnaires (ASQ); Disruptive Behavior Disorders (DBD) Rating Scale; Conners' Continuous Performance Test (CPT) and Woodcock-Johnson Psycho-Educational Battery Revised (WJ-R) (cognitive function)	IN PEDIATRIC AGE: supplementation group received eight capsules of PUFA (60 mg DHA, 10 mg EPA, 5 mg AA, 12 mg GLA, and 3 mg vitamin E per capsule) and placebo group received 8 capsules (0.8 g olive oil per capsule) per day		----	At the end of intervention, a clear significant benefit from PUFA supplementation for all behaviors characteristic of AD/HD was not observed ($p > 0.05$). However, attention symptoms were significantly improved according to teacher ($p = 0.03$), comparing to placebo.
ADHD	Yorgidis, E. et al., 2021[35]	Open trial (22 weeks)	Germany	n = 16 | 7 - 13 years | 18.8 % female	Diagnostic: ICD-10, Kiddie-SADS-Present and Lifetime Version (K-SADS-PL) | Symptomatology: ADHD rating scale IV (ARS); Abbreviated Conners´ Scale (ACS)	IN PEDIATRIC AGE: (T0-T1): daily 24h-recalls, 2 weeks (T1-T2): administration of an oligoantigenic diet, 4 weeks T2-T4): reintroduction of usually consumed foods, 16 weeks	n = 16 (100 %)	---	After 4 weeks of oligoantigenic diet, it was observed a significant reduction of ARS total score ($p < 0.0001$), compared to baseline. This effect was more significative when diet included milk products, corn, and wheat.
ADHD	Stadler, D. D. et al., 2016[85]	Case-control study	USA	n = 474 | 7 – 13 years | 36 % female	Diagnostic: DSM-V criteria | Symptomatology: ADHD Rating Scale (ARS)	IN PEDIATRIC AGE: assessment of breastfeeding duration retrospectively by a single item on the developmental history form	n = 291 (61.4 %)	---	An association between shorter breastfeeding duration and more child total ADHD symptoms was found ($p < 0.05$).
ADHD	van Egmond-Fröhlich, A. W. et al., 2012[91]	cross-sectional study	Germany	n = 9428 | 6-17 years | no information about gender	Diagnostic: Parent-rated Strengths and Difficulties Questionnaire (SDQ); Symptomatology: SDQ	IN PEDIATRIC AGE: dietary assessment with a semi-quantitative food frequency questionnaire (FFQ); diet quality assessed with Healthy Nutrition Score for Kids and Youth (HuSKY)	n = 1272 (13,5 %)	---	SDQ-HI scores were significantly and positively associated with average energy density of food, volume of beverages and total energy intake ($p < 0.001$) and negatively associated with the HuSKY diet quality index ($p < 0.001$).

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ADHD	Rucklidge, J. J. et al., 2019[36]	RCT (10 weeks)	New Zealand	n = 71 |9.7 ± 1.5 years | 33 % female	Diagnostic: Kiddie Schedule for Affective Disorders and Schizophrenia Lifetime Version (K-SADS-PL); Parent and Teacher Conners Rating Scales | Symptomatology: ADHD Rating Scale IV (ADHD-RS-IV); Clinical Global Impressions - Improvement (CGI-I) ratings (response to treatment); Children's Global Assessment Scale (CGAS) (functioning)	IN PEDIATRIC AGE: supplementation with micronutrient formula (Daily Essential Nutrients - DEN) of 3 capsules per day, with a gradual increase up to 12 capsules a day on 7th day	n = 71 (100 %)	---	There were no significant improvements in ADHD outcomes after the 10-week treatment, compared to baseline.
ADHD	Schmidt, M. H. et al., 1997[37]	RCT (9 days)	Germany	n = 49 |6-12 years| 4 % female	Diagnostic: DSM-III and ICD-10 | Symptomatology: Paired Associate Learning Task (PAT) and Continuous Performance Task (CPT) (performance evaluation); Conners Abbreviated Parent-Teacher Questionnaire (behavior evaluation)	IN PEDIATRIC AGE: oligoantigenic diet during 9 days with assessment at day 3 and 8	n = 49 (100 %)	---	Twelve children (24 %) showed significant behavioral ratings improvement (> 25 %) in standardized play situations and test situations during intervention diet, relative to control diet conditions ($p < 0.05$).
ADHD and Learning disabilities	Park, S. et al., 2012[10]	Cross-sectional study	Korea	n = 986 | 9.1 ± 0.7 years | 48.6% female	Diagnostic: DSM-IV and Learning Disability Evaluation Scale (LDES) | Symptomatology: Child Behavior Checklist (CBCL); Korean Educational Development Institute's Wechsler Intelligence Scales for Children (KEDI-WISC) (cognitive function)	IN PEDIATRIC AGE: children's diet assessed with the mini-dietary assessment for Korean	n = 45 (4.6 %)	---	A high intake of sweetened desserts, fried food and salt is significantly associated with more learning, attention and behavioral problems, whereas a balanced diet, regular meals and a high intake of dairy products and vegetables is significantly associated with less learning, attention, and behavioral problems ($p < 0.01$).

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ADHD and ASD	Boucher, O. et al., 2016[86]	Cohort study (4 years follow-up)	Spain	n = 1346 | 0 - 6.9 years | 50 % female	ADHD symptomatology: DSM-IV) | ASD diagnostic: Childhood Autism Spectrum Test (CAST)	IN PEDIATRIC AGE: diet report using interviewer-administered questionnaires when children were 6 months, 14 months, and 4 years old.	ADHD: n = 69 (5 %) | ASD: n = 70 (5 %)	---	Longer duration of breastfeeding was independently associated with fewer autistic traits (β = -0.08, 95 % CI: - 0.16, -0.00). Breastfeeding was not related to ADHD symptoms (β = -0.02, 95% CI: - 0.04, 0.01)
ASD	Kerley, C. P. et al., 2017[38]	RCT (20 weeks)	Ireland	n = 38 | 6.9 ± 3.8 years (placebo); 7.9 ± 2.3 years (interven-tion) 13 % female	Symptomatology: Developmental Disabilities—Children's Global Assessment Scale (DD-CGAS) (Self-care, Communication, Social behavior and School/academic subscale)	IN PEDIATRIC AGE: 2000 IU vitamin D3 supplementation or placebo daily	n = 38 (100 %)	---	No significant differences were observed in behavior scores (p > 0.05). However, a significant improvement was observed in self-care score on DD-CGAS in vitamin D3 group (n = 18), compared to placebo group (n = 20) (p = 0.02).
ASD	Alessandria, C. et al., 2019[39]	Cohort study (6 months follow-up)	Italy	n = 130 | 10.4 ± 6.6 years |17 % females	Diagnostic: DSM-IV | Symptomatology: medical history and physical examination	IN PEDIATRIC AGE: gluten/casein-free diet (GCFD) reporting by a 3-day dietary recall	n = 151 (100 %)	---	Symptoms improvement was not significantly associated to GCFD (p > 0.05), namely Constipation, Diarrhea, Abdominal pain, dysphagia, Macroscopic malabsorption, Food selectivity, Vomit and Flatulence.
ASD	Alomar, R. S. et al., 2021[82]	Case-control study	Saudi Arabia	n = 200 | 3-10 years | 35.5 % females	Diagnostic: DSM-V | Symptoms: Childhood Autism Rating Scale (CARS) (severity)	IN PEDIATRIC AGE: vitamin D diet intake reported by a specially designed questionnaire	n = 100 (50 %)	---	74.19 % (n = 23) of severely autistic children, 60.87 % (n = 42) mild to moderate autistic children and 34% (n = 34) normal children had a deficient vitamin D intake. It was found a negative association between a vitamin D rich diet and mild to moderate degree of autism (symptom level) (OR = 0.27, 95 % CI = 0.12-0.57)

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ASD	Afzal, N. et al., 2003[92]	Case-control study	United Kingdom	n = 132 | 2.2–18.7 years | 21.2 % females	Diagnostic: DSM-IV | Symptomatology: constipation symptoms using a validated index (≥ 9 points in a score)	IN PEDIATRIC AGE: dietary history extracted from clinical records: Combined diary- and gluten-free diets; dairy-free diet; gluten-free diet	n = 103 (78 %)	---	Consumption of milk was the strongest predictor of constipation in the autistic group (n = 103) ($p < 0.01$). Gluten consumption was not associated with constipation in this group ($p > 0.05$).
ASD	Raghavan, R. et al., 2018[78]	Cohort study (12 years follow-up)	USA	n = 1257 | 5 - 17 years | 53 % female	Diagnostic: previously obtained	IN PREGNANCY: multivitamin supplementation was assessed via questionnaire interview.	n = 86 (7 %)	Low (≤ 2 times/week) and high (> 5 times/week) supplementation was associated with increased risk of having ASD comparing to moderate (3-5 times/week) self-reported supplementation during pregnancy.	---
ASD	Piwowarczyk, A. et al., 2020[40]	RCT (6 months)	Poland	n = 66 | 36-69 months | 15.2 % female	Diagnostic: DSM-V | Symptoms: Social Communication Questionnaire; Autism Spectrum Rating Scale	IN PEDIATRIC AGE: intervention group: 6 months run-in period on a gluten-free diet (GFD) | control group: gluten-containing diet	n = 66 (100 %)	---	There were no differences in autistic symptoms, maladaptive behaviors, or intellectual abilities after the intervention ($p > 0.05$), between GFD group (n = 28) and control group (n = 30)
ASD	Levine, S. Z. et al., 2018[7]	Cohort study (8-12 years follow up)	Israel	n = 45300 | 0-12 years | 48,8 % female	Diagnostic: ICD-9	IN PREGNANCY: consumption of folic acid (vitamin B9) and multivitamin supplements (Anatomical Therapeutic Chemical A11 codes vitamins A, B, C, and D) before and during pregnancy	n = 572 (1.3 %)	Maternal exposure to folic acid and multivitamin supplements were significantly associated with a lower likelihood of having ASD, compared with no exposure, before and during pregnancy ((RR, 0.39; 95% CI, 0.30-0.50), (RR, 0.27; 95% CI, 0.22-0.33), respectively)	---

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ASD	Navarro, F. et al., 2015[41]	RCT (4 weeks)	USA	n = 12 | 4-7 years | no information about gender	Diagnostic: DSM-IV | Symptoms: lactulose: mannitol (L/M) sugar permeability test (intestinal permeability); Aberrant Behavior Checklist (ABC); Conner's Parent Rating Scale (CPRS) (behavior)	IN PEDIATRIC AGE: gluten-dairy free diet vs. placebo	n = 12 (100 %)	---	Neither the L/M ratio nor behavioral scores were different between groups exposed to gluten/dairy (n = 6) or placebo (n = 6) (p = 0.307 and p = 0.292, respectively)
ASD	Levy, S. E. et al., 2007[42]	Cross-sectional study	USA	n = 62 | 3-8 years | 10,4 % female	Diagnostic: DSM-IV | Symptoms: parental self-report (gastrointestinal symptoms)	IN PEDIATRIC AGE: 3-day reported diet by parents (further calculation of total calories, protein, carbohydrate, and fat intake)	n = 62 (100 %)	---	No statistically significant relationships between stool consistency (gastrointestinal symptoms) and total calories, protein, carbohydrate, and fat intake were observed (p > 0.05).
ASD	Li, Y. M. et al., 2018[79]	Case-control study	China	n = 708 | 3-6 years | 52,5 % female	Diagnostic: DSM-IV	IN PREGNANCY: questionnaire by interview about diet, obtaining information about 3 dietary patterns: mostly meat, mostly vegetables or both	n = 354 (50 %)	Mostly meat and mostly vegetables dietary patterns during pregnancy were associated with a significant increased risk of ASD in offspring (OR: 3.975; 95% CI: 1.202, 13.148), (OR: 2.134; 95% CI: 1.138, 4.001), respectively).	---

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ASD	Chan, A. S. et al., 2012[110]	RCT (1 month)	China	n = 24 | 7-17 years | 16.7 % females	Diagnostic: DSM-IV | Symptomatology: Autism Diagnostic Interview Revised (ADI-R)	IN PEDIATRIC AGE: placebo or dietary modifications including reduced intake of ginger, garlic, green onion, spicy foods, eggs, meat, and fish	n = 13 (54,2 %)	---	After 1 month of modification in diet: The experimental group (n = 12) showed significantly improved performance in mental flexibility, response inhibition and planning ($p < 0.05$), comparing to baseline. Parents of the children from experimental group also reported a significant reduction of social communication problems and repetitive, inflexible, and hyperactive behaviors ($p < 0.05$), comparing to baseline.
ASD	DeVilbiss, E. A. et al., 2017[80]	Cohort study (4-15 years follow-up)	Sweden	n = 273,107 | 0-15 years | 48,7 % female	Diagnostic: DSM-IV	IN PREGNANCY: multivitamin, iron, and folic acid supplementation during pregnancy, self-reported at the first antenatal visit.	n = 6115 (2,3 %)	Maternal multivitamin use with or without additional iron or folic acid, or both was associated with lower odds of ASD with intellectual disability in children, compared with mothers who did not use multivitamins, iron, and folic acid (OR = 0.69, 95% CI = 0.57 - 0.84). There was no consistent evidence that either iron or folic acid use were inversely associated with ASD prevalence.	---

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ASD	Elder, J. H. et al., 2006[43]	RCT (12 weeks)	USA	n = 15 | 2-16 years | 20 % female	Diagnostic: DSM-IV | Symptomatology: Childhood Autism Rating Scale (CARS); Ecological Communication Orientation Scale (ECOS); Direct behavioral observation	IN PEDIATRIC AGE: regular diet vs Gluten- and casein-free diet (GFCF)	n = 15 (100 %)	---	Group analysis results indicated no significant differences between regular diet and GFCF diet in CARS ($p = 0.85$), ECOS ($p = 0.29$), or behavioral frequencies ($0.32 < p < 0.45$) even though several parents reported improvement of child language, decreased hyperactivity, and decreased tantrums in their children.
ASD	Ghalichi, F. et al., 2016[44]	RCT (6 weeks)	Iran	n = 76 | 7.92 ± 3.37 years | 26.3 % female	Diagnostic: Autism Diagnostic Interview-Revised (ADI-R) | Symptomatology: ROME III questionnaire; Gilliam Autism Rating Scale 2 questionnaire (GARS-2)	IN PEDIATRIC AGE: regular diet vs Gluten-free diet (GFD), consisting of gluten free pasta, biscuits, and breads, according to age requirements	n = 76 (100 %)	---	In the GFD group (n=38), the prevalence of gastrointestinal symptoms including stomachache, bloating and constipation (according to Rome III) and behavioral outcomes including stereotyped behaviors, communication, and social interaction (according to GARS-2), decreased significantly after 6 weeks of intervention, compared to baseline ($p < 0.05$).
ASD	González-Domenech, P. J. et al., 2020[45]	RCT (1 year)	Spain	n = 37 | 8.9 ± 4.0 years | 46 % female	Diagnostic: ICD-10 | Symptomatology: Autism Treatment Evaluation Checklist (ATEC) Scale; Behavioral Summarized Evaluation (ERC-III) Scale	IN PEDIATRIC AGE: normal diet vs gluten- and casein-free (GFCF)	n = 37 (100 %)	---	When both groups were analyzed, a non-significant decrease was found in the scores of ATEC Scale and ERC-III Scale, after 6 months of intervention ($p > 0.05$). The GFCF diet did not induce significant changes in behavioral symptoms of autism ($p > 0.05$).

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ASD	Hyman, S. L. et al., 2016[46]	RCT (30 weeks)	USA	n = 14 | 3-5 years | 14.3 % female	Diagnostic: Autism Diagnostic Interview (ADI-R); Autism Diagnostic Observation Schedule (ADOS) | Symptomatology: Bristol Stool Scale (Physiologic Functioning); Conner's Abbreviated Rating Scale (attention), Ritvo-Freeman Real Life Rating Scales (ASD behavior)	IN PEDIATRIC AGE: Implementation phase: gluten-free/casein-free (GFCF) diet consumption for 4-6 weeks; Challenge Phase: (foods that contained gluten only, casein only, both gluten and casein, or neither (placebo)) once per week for 12 weeks; Maintenance Phase: Families were free to maintain, modify, or abandon the GFCF diet during 12 more weeks.	n = 14 (100 %)	---	Dietary challenges did not have statistically significant effects on measures of physiologic functioning, behavior problems, or autism symptoms, between the day before the challenge, the day of the challenge and after the challenge, compared to placebo ($p > 0.05$).
ASD	Feng, J. et al., 2017[83]	RCT (6 months)	China	n = 500 | 4.76 ± 0.95 years (ASD group); 5.12 ± 1.15 years (control group) | 20.4 % female	Diagnostic: DSM-IV | Symptoms: Autism Behavior Checklist (ABC); Childhood Autism Rating Scale (CARS).	IN PEDIATRIC AGE: vitamin D3 supplementation intramuscularly administered at a dosage of 150 000 IU per month (for 3 months) and orally administered at a dosage of 400 IU per day (for 3 months)	n = 215 (43 %)	---	In ASD group (n = 215), ABC subscales (social skills, body and object use, language, social or self-help), and total CARS scores were reduced significantly, in comparison to the situation before treatment ($p < 0.05$).
ASD	Harris, C. et al., 2012[47]	Cross-sectional study	USA	n = 13 | 9 ± 1.9 years | 30.8 % female	Diagnostic: previously obtained | Symptomatology: Gastrointestinal Symptoms Rating Scale (GSRS); Childhood Autism Rating Scale (CARS)	IN PEDIATRIC AGE: gluten- and casein-free diet (GFCF), evaluated with a food frequency questionnaire	n = 13 (100 %)	---	GSRS and CARS scores did not differ significantly according to diet ($p > 0.05$) between GFCF group (n = 7) and non-GFCF diet group (n = 6). Parents of all the children on a GFCF diet (n = 7) reported improved GI symptoms and behavior patterns.

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ASD	Inoue, R. et al., 2019[48]	Clinical trial (15 months)	Japan	n = 13 | 5.9 ± 2.2 years | 7.7% female	Diagnostic: DSM-V; Pervasive Developmental Disorders Autism Society Japan Rating Scale (PARS); Modified Checklist for Autism in Toddlers (M-HAT) | Symptomatology: feces and serum collection; Aberrant Behavior Checklist - Japanese Version (ABC-J) (behavioral irritability)	IN PEDIATRIC AGE: supplementation with partially hydrolyzed guar gum (PHGG) (guar gum with b-endogalactomannase produced by a strain of Aspergillus niger)	n = 13 (100 %)	---	supplementation with partially hydrolyzed guar gum significantly increased the frequency of defecation per week ($p < 0.01$) and significantly improved behavioral irritability as per the ABC-J ($p < 0.01$), compared to pre-supplementation.
ASD	Javadfar, Z. et al., 2020[49]	RCT (15 weeks)	Iran	n = 43 | 3-13 years | 16.3 % female	Diagnostic: DSM-V | Symptoms: Autism Rating Scale (CARS); The Autism Treatment Evaluation Checklist (ATEC); Aberrant Behavior Checklist Community (ABC-C)	IN PEDIATRIC AGE: placebo or vitamin D supplementation (300 IU/kg daily up to a maximum of 6000 IU/d vitamin D syrup)	n = 43 (100 %)	---	In vitamin D group (n = 22), the clinical symptoms of autism measured by CARS and ATEC scales were alleviated significantly ($p = 0.021$ and $p = 0.020$, respectively), compared to placebo group (n = 21), after 15 weeks; At the end of the study, no significant difference was detected in ABC-C score between the two groups ($p > 0.05$).
ASD	Mazahery, H. et al., 2019[50]	RCT (12 months)	New Zealand	n = 73 | 2.5–8 years | 17.8 % female	Diagnostic: DSM-V | Symptomatology: The Aberrant Behavior Checklist (ABC)	IN PEDIATRIC AGE: placebo or consumption of Vitamin D3 (2000 IU/day), omega-3 LCPUFA (722 mg DHA/day)	n = 73 (100 %)	---	After 12 months, children receiving omega-3 (n = 23) and Vitamin D (n = 19) had greater reduction in irritability than placebo ($p = 0.001$ and $p = 0.01$, respectively). Compared to placebo, children on the vitamin D group also had greater reduction in hyperactivity, comparing to placebo ($p = 0.047$).

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ASD	Mazahery, H. et al., 2019[51]	RCT (12 months)	New Zealand	n = 73 | 2.5–8 years | 17.8 % female	Diagnostic: DSM-V | Symptomatology: Social Responsiveness Scale (SRS); Sensory Processing Measure (SPM)	IN PEDIATRIC AGE: placebo or consumption of Vitamin D3 (2000 IU/day), omega-3 LCPUFA (722 mg DHA/day)	n = 73 (100 %)	---	Compared to placebo (n=29): Children who received omega-3 (n = 23) and vitamin D + omega-3 (n = 15) showed significant improvements in SRS- social awareness ($p = 0.03$) and a trend for improvements in SRS-social communicative functioning and SPM-taste/smell ($p < 0.1$). It was also found a trend for improvements in children who received omega-3 for SRS - total score and SPM - balance/motion score ($p < 0.1$).
ASD	Mehrazad-Saber, Z. et al., 2018[52]	RCT (2 months)	Iran	n = 43 | 4-16 years | 27.9 % female	Diagnostic: DSM-IV | Symptoms: Gilliam Autism Rating Scale 2 (GARS-2); Children's Sleep Habits Questionnaires (sleep disorders)	IN PEDIATRIC AGE: 500 mg of carnosine supplementation or 500 mg of placebo per day	n = 43 (100 %)	---	after 2 months of carnosine supplementation (n = 21), there was no significant effect on autism severity ($p > 0.05$), whereas it significantly reduced sleep duration ($p = 0.04$), parasomnias ($p = 0.02$) and total sleep disorders score ($p = 0.006$) when compared with the control group (n = 22)
ASD	Nogay, N. H. et al., 2021[53]	RCT (2 weeks)	USA	n = 15 | 11.7 ± 3.3 years | 33.3 % female	Diagnostic: previously obtained | Symptoms: Aberrant Behavior Checklist-Community (ABC-C); Pediatric Quality of Life Inventory (PedsQL) (gastrointestinal)	IN PEDIATRIC AGE: placebo or low FODMAP diet, evaluated with a 3-day dietary record	n = 15 (100 %)	---	The low FODMAP diet group (n = 7) had significant less GI symptoms, compared to the control group (n = 8) at follow-up ($p < 0.05$). However, there were no significant differences in behavioral problems between these groups ($p > 0.05$), after intervention.

Attachment A (continued)

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ASD	Ooi, Y. P. et al., 2015[54]	Open-label trial (12 weeks)	Singapore	n = 41 | 11.66 ± 3.05 years | 12.2 % female	Diagnostic: DSM-IV | Symptoms: The Social Responsiveness Scale Parent (SRS-P); Child Behavior Checklist (CBCL)	IN PEDIATRIC AGE: 15 ml liquid (Efamol Efalex) twice daily, which consists of 1 g/day of omega-3 fatty acids (840 mg DHA, 192 mg EPA, 1278 mg pure evening primrose oil of which: 66 mg arachidonic acid (AA) and 144 mg gamma linolenic acid, 60 mg vitamin E, and 3 mg thyme oil)	n = 41 (100 %)	---	At post-treatment, participants showed significant improvements in all subscales of the SRS ($p < 0.01$) and in Social and Attention Problems syndrome scales of the CBCL ($p < 0.05$), compared to baseline period.
ASD	Pennesi, C. M. et al., 2012[55]	Cross-sectional study	USA	n = 387 | children, no information about age | 18% female	Diagnostic: previously obtained | Symptomatology: online questionnaire (ASD behaviors, physiological symptoms, and social behaviors	IN PEDIATRIC AGE: assessment of gluten-free, casein-free diet (GFCF) diet implementation by a 90-item online questionnaire applied in parents	n = 387 (100 %)	---	Parental report of GFCF diet implementation showed a significant improvement in ASD behaviors, physiological symptoms, and social behaviors ($p < 0.05$) with dietary treatment.
ASD	Silva, D. V. et al., 2020[56]	Cross-sectional study	Brazil	n = 39 | 3-10 years | 15.4% female	previous diagnostic of ASD | gastrointestinal symptoms assessed by a questionnaire concerning the occurrence of diarrhea, constipation, bloating, gas, nausea, vomiting and gastroesophageal reflux in the previous 30 days prior to the survey	IN PEDIATRIC AGE: evaluation of food intake in the past 24 hours of the interview, categorized into: gluten sources, casein sources, and ultra-processed foods.	n = 39 (100 %)	---	In this sample (n = 3), only gluten consumption was associated with gastrointestinal manifestations (β = 0.38; 95% CI 0.07-0.75; p = 0.02). Casein and ultra-processed foods were not associated with gastrointestinal symptoms ($p > 0.05$).
ASD	Whiteley, P. et al., 2010[57]	RCT (8-24 months)	Denmark	n = 55 | 4-10.9 years | 10.9 % female	Diagnostic: ICD-10 | Symptomatology: Autism Diagnostic Observation Schedule (ADOS); Gilliam Autism Rating Scale (GARS); Attention-Deficit Hyperactivity Disorder – IV rating scale (ADHD-IV) (Inattention and hyperactivity)	IN PEDIATRIC AGE: placebo or gluten and casein-free diet during 8, 12, 20 or 24 months	n = 55 (100 %)	---	children in the diet group (n = 27) showed a significant improvement at 12 months, in social interaction ($p = 0.0001$), inattention ($p = 0.0007$) and hyperactivity ($p = 0.0188$), compared to baseline.

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ASD	Şengüzel, S. et al., 2021[58]	Cross-sectional study	Turkey	n = 46 | 2-10 years | 17.4 % females	Diagnostic: previously obtained | Symptomatology: Autism Behavior Checklist (ABC); Brief Autism Mealtime Behavior Inventory (BAMBI)	IN PEDIATRIC AGE: food consumption assessed with a Food Frequency Questionnaire	n = 46 (100 %)	---	Consumption of milk was associated with higher BAMBI autism scores (r= -0.388, *p* = 0.008); consumption of oily seeds was associated with a higher ABC sensorial score (r = -0.338, *p* = 0.022); not consuming fresh fruits was associated with higher ABC relating scores (r=0.317, *p* = 0.032); no yoghurt consumption was associated with higher ABC language scores (r=0.302, *p* = 0.042)
ASD	Sun, C. et al., 2016[59]	Open-label trial (3 months)	China	n = 66 | 57.23 ± 15.06 months | 18.2 % female	Diagnostic: DSM-IV | Symptomatology: Autism Behavior Checklist (ABC), Childhood Autism Rating Scale (CARS); Autism Treatment Evaluation Checklist (ATEC); Psychoeducational Profile-3 (PEP-3)	IN PEDIATRIC AGE: 400 µg folic acid supplementation twice a day (a total of 800 µg/day)	n = 66 (100 %)	---	Folic acid supplementation in intervention group (n = 44) improved autism symptoms towards sociability, cognitive verbal/preverbal, receptive language, affective expression, and communication, compared to baseline ($p < 0.05$)
ASD	Taliou, A. et al., 2013[60]	Open-label pilot study (26 weeks)	Greece	n = 40 | 79.94 ± 20.08 months | 12.5 % female	Diagnostic: DSM-IV | Symptomatology: Vineland Adaptive Behavior Scales (VABS); Aberrant Behavior Checklist (ABC); Autism Treatment Evaluation Checklist (ATEC); Clinical Global Impression-Improvement score (CGI-I).	IN PEDIATRIC AGE: 1 soft gel capsule/10 kg (22 lb.) weight/day with food for 26 weeks, each capsule containing: 2 flavonoids (>95% pure), 100 mg luteolin from chamomile, 70 mg quercetin and 30 mg quercetin glycoside rutin from the Sophora japonica leaf.	n = 40 (100 %)	---	In this sample (n = 40), there was a significant improvement in adaptive functioning as measured by the VABS scores ($p < 0.005$), as well as in overall behavior as indicated by the reduction in ABC subscale scores ($p < 0.05$) after 26-weeks supplementation, compared to baseline.

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ASD	Tan, M. et al., 2020[81]	Clinical trial (24 weeks)	China	n = 617 | 4.68 ± 1.94 years (ASD group); 4.47 ± 1.06 years (control group) | 22 % female	Diagnostic: DSM-V | Symptomatology: Autism Behavior Checklist (ABC); Childhood Autism Rating Scale (CARS); Social Responsiveness Scale (SRS)	IN PREGNANCY: supplementation with folic acid or micronutrient supplements during 2 to 4 weeks	n = 416 (67.4 %)	compared with the children whose mothers used FA supplementation during pregnancy, the children whose mothers did not use FA supplementation had an increased risk of ASD (OR) = 1.905, 95% CI: 1.238–2.933, p = 0.003), as well as children born to a mother who did not use micronutrient supplements during pregnancy, compared with children whose mother did (OR = 1.718, 95 % CI: 1.196–2.468, p = 0.003).	---
ASD	Voigt, R. G. et al., 2014[61]	RCT (6 months)	USA	n = 48 | 6.1 ± 2.0 years | 17 % female	Diagnostic: DSM-IV | Symptomatology: Child Development Inventory (CDI); Aberrant Behavior Checklist (ABC); Behavior Assessment Scale for Children (BASC)	IN PEDIATRIC AGE: daily supplementation during 6 months with triglyceride oil capsule containing 200 mg DHA from algal oil + 300 mg oleic acid sunflower oil; placebo capsule: 250 mg of corn oil + 250 mg of soybean oil.	n = 48 (100 %)	---	DHA group (n = 24) did not significantly improve in core symptoms of autism on the CGI-I, CDI or ABC compared to placebo group (n = 24) after 3 or 6 months of treatment (p > 0.05). Significant improvements were found in only 2 items (parent- social skills and teacher - functional communication) of the BASC scale (p < 0.05) after 6 months of treatment, compared to placebo group.

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Tourette Syndrome (TS)	Rizzo, R. et al., 2022[71]	Open label trial (pilot study) (2 months)	Italy	n = 34 | 4-17 years | 11.8 % female	Diagnostic: DSM-V | Symptomatology: Yale Global Tic Severity Scale (YGTSS); Children's Yale-Brown Obsessive-Compulsive Scale for Children (CY-BOCS); Anxiety Scale for Children (MASC) (anxiety)	IN PEDIATRIC AGE: nutritional supplementation with L-Theanine (200 mg/day) and vitamin B6 (2.8 mg/day) vs. placebo (psychoeducation)	n = 34 (100 %)		After 2 months, supplementation with L-Theanine and vitamin B6 was significantly more effective than psychoeducation in reducing severity of tics, anxiety, and co-occurring disorders in supplementation group (n = 17), compared to placebo group (n = 17) as measured by neuropsychological findings (p < 0.05).
Autosomal trisomy	Botto, L. D. et al., 2004[72]	Case-control study	USA	n =2976 | 2-16 years | no information about gender	Diagnostic: Down syndrome (trisomy 21), trisomy 18 and trisomy 13 previously diagnosed	IN PREGNANCY: multivitamin use 3 months before and 3 months into pregnancy was asked through a structured questionnaire	n = 197 (0.1 %)	Multivitamin use was not associated with a major reduction in the risk for common autosomal trisomy (OR = 0.9, 95% C I= 0.6-1.3), Compared to no such use.	---
Bipolar Disorder (PBD) and ADHD	Rucklidge, J. J. et al., 2010[73]	Clinical trial (6 months)	Canada	n = 161| 7-18 years | 40,8 % female	Diagnostic: previously obtained | Symptomatology: The Self-Monitoring Form (DSM-specified mood symptoms and ADHD index)	IN PEDIATRIC AGE: supplementation with a 36-ingredient micronutrient formula (EMPowerplus) for 3-6 months	Children with only PBD = 91 (56,5 %); children with PBD and ADHD = 29 (18 %); children with only ADHD = 41 (25,5 %)	---	At follow-up, the mean of bipolar symptom's severity was 44% lower than baseline (p < 0.001) in children with only PBD. In children with both PBD and ADHD, there was a 43 % decline in bipolar symptoms and 40 % in ADHD symptoms, compared to baseline (p < 0.002). Children with only ADHD showed a 47 % reduction in symptoms from baseline to follow-up (p < 0.001).
Dyslexia	Lindmark, L. et al., 2007[67]	Open pilot study (5 months)	Sweden	n=17 | 9-17 years | 33 % female	Diagnostic: previously obtained | Symptomatology: objective word-chain test	IN PEDIATRIC AGE: 8 capsules per day of a long-chain polyunsaturated fatty acid (LC-PUFA) supplement containing high-DHA fish oil and evening primrose oil	n = 17 (100 %)	---	13 of 17 children (76.4 %) had a significant improvement on the word-chain test (p = 0.04). Reading speed improved by 60% after supplementation, compared to baseline (p = 0.01).

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Dyslexia	Kairaluoma, L. et al., 2009[68]	RCT (90 days)	Finland	n = 61 | 10.6 ± 1.1 years | 42.6 % female	Diagnostic: Standardized reading test - Lukilasse (≥ 4 standard points below age level) + intelligence quotient (IQ) >80 | Symptoms: Word and Pseudo-word Reading tasks; Text-reading task; Spelling subtest of Lukilasse; Standardized test for decoding fluency; Rapid Serial Naming test; Wechsler Intelligence Scale for Children-III	IN PEDIATRIC AGE: Ethyl-EPA (500 mg/day) and carnosine (400 mg/day) supplementation vs. placebo	n = 61 (100 %)	---	There were no statistical differences between EPA group (n = 30) and Placebo (n = 31) in reading accuracy, speed measured on any of the four reading tests, spelling, decoding fluency, arithmetical skills, language skills and in teacher and parental assessments of attention and behavior problems (p > 0.05).
Epilepsy	Ijff, D. M. et al., 2016[69]	RCT (19 weeks)	The Nether-lands	n = 50 | 1.1 - 16.5 years | 42 % female	Diagnostic: previously obtained | Symptomatology: Profile of Mood States (POMS) questionnaire; Peabody Picture Vocabulary test (PPVT-III-NL); Hague Restrictions in Childhood Epilepsy Scale (HARCES); Personal Adjustment and Role Skills Scale III (PARS-III) questionnaire	IN PEDIATRIC AGE: ketogenic diet (KD) vs control diet	n = 50 (100 %)	---	At the 4-month follow-up, KD group (n = 28) had a higher score on the subscale "vigor" ('energy') in POMS, a significant seizure reduction according to HARCES rating, a higher score on the subscale 'productivity' in PARS-III, less anxious and mood-disturbed behavior on SEV subscale, compared to the control group (n = 22) (p < 0.05).
Epilepsy	Hallböök, T. et al., 2015[70]	Cohort study (2 years follow-up)	Denmark, Norway, and Sweden	n = 290 | 5.3 years (median age at diet introduction) | 49.3% female	Diagnostic: International League Against Epilepsy (ILAE); | Symptomatology: seizure frequency	IN PEDIATRIC AGE: ketogenic diet at a 3:1 or 4:1 ratio calculated on an individual basis by a dietitian and fully supplemented with vitamins and minerals (follow-ups at 3, 6, 12 and 24-month)	n = 290 (100 %)	---	The association between the Ketogenic Diet and seizure reduction was statistically significant at 3, 6 and 12 months (p < 0.05) (n = 290), compared to number of seizures at the start of treatment.

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Intellectual Disability	Gore, N. et al., 2015[74]	Cross-sectional study (integrated in a Cohort Study)	United Kingdom	n = 18504 | 7 years | no information about gender	Diagnostic and Symptomatology: Bracken School Readiness Assessment (≥ 2 standard deviations below the mean for diagnostic); British Ability Scales (BAS) Naming Subscale	IN PEDIATRIC AGE: maternal self-reported breastfeeding habits when the child was 9-months old.	n = 539 (3 %)	---	Those who were ever breastfed (n = 13085), breastfed at 3 months (n = 7155), exclusively at 3 months (n = 4701) and breastfed at 6 months (n = 4353) have less intellectual disability symptoms at 9 months ($p < 0.001$), compared to children without breast-feeding (OR: 0.56, CI: 0.47–0.67; OR: 0.50, CI:0.41–0.61; OR: 0.53, CI:0.42–0.68, OR: 0.53, CI:0.42–0.68, respectively).
Learning disabilities	Carlton, R. M. et al., 2000[62]	RCT (1 year)	USA	n =19 | 7-14 years | 30% female	Diagnostic: New Work State criteria; previous records; psychoeducational tests (Wechsler Intelligence Scale for Children; Wide Range Achievement Test, Detroit Test of Learning Aptitude, Test of Written Language, Woodstock Reading Mastery, Coopersmith Self-Esteem Inventory, Standford Achievement Test, Bender-Gestalt) | Symptomatology: Parent-reported behavior and psychoeducational tests	IN PEDIATRIC AGE: placebo vs. bottle containing 1 of the 3 nutrients: magnesium, pyridoxine, and ascorbic acid according to the recommended daily allowance	n = 19 (100 %)	---	Some children gained 3 to 5 years in reading comprehension within the first year of treatment. All children in special education classes had their grades grown significantly ($P < 0.01$).

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Learning disabilities (ADD/ADHD, tutoring for reading, math, attending summer school, special class placement, Individualized Education Plan, repeating a grade, and low educational attainment)	Carwile, J. L. et al., 2016[63]	Cohort study	USA	n =1689 | 7-13 years | 73 % female	Diagnostic and symptomatology: self-administered questionnaires	IN PEDIATRIC AGE: fish consumption reported in self-administered questionnaires	n = 451 (27 %)	---	participants who ate fish several times a week had an elevated odds of ADD/ADHD (odds ratio: 5.2; 95% confidence interval: 1.5–18) compared to participants who did not eat fish.
Learning disabilities (extreme difficulty in reading and spelling, dyslexia, and other behavioral problems)	Thiessen, I. et al., 1975[65]	Clinical Trial (12 weeks)	USA	n = 33 | 7.5 - 14.9 years | 24,2 % female	Diagnostic: extreme difficulty in reading and spelling, with or without other behavioral problems | Symptomatology: Illinois Test of Psycholinguistic Ability (sensory function); The Glen Green Perceptual Dysfunction Questionnaire (behavior)	IN PEDIATRIC AGE: administration of mega doses of vitamins, daily: 3 g ascorbic acid, 3 g niacinamide, 250 mg Pyridoxine, and 250 mg pantothenic acid for 12 weeks.	n = 24 (72,7 %)	---	No significant changes were observed in reading and spelling levels in experimental group (n = 24) after intervention, compared with control (n = 9) (p > 0.05). However, there was an improvement in the reduction in hyperkinesis, sleep disturbance, and nystagmus in experimental children receiving mega doses of vitamins C, B-sub-3, pantothenic acid, and B-sub-6 (plus a high-protein low-carbohydrate diet), compared to control group (p < 0,05).
Specific learning difficulties (weak working memory and phonological processing, specific reading difficulties, dyslexia)	Richardson, A. J. et al., 2002[64]	RCT (2 weeks)	United Kingdom	n = 41 | 10.25 ± 0.74 years | 14.6 % female	Diagnostic: DSM Inattention, DSM Hyperactive –Impulsive and DSM Combined-type scores above age; Conners' Parent Rating Scale (CPRS-L) | Symptomatology: CPRS-L (behavior and learning problems)	IN PEDIATRIC AGE: intervention group: n-3 and n-6 PUFA supplementation for 2 weeks containing, daily: 186 mg EPA, 480 mg DHA, 96 mg γ-linolenic acid, 60 IU vitamin E, 864 cis-linoleic acid, 42 mg AA and 8 mg thyme oil | placebo group: olive oil	n = 41 (100 %)	---	after 12 weeks: mean scores for cognitive problems and general behavior problems were significantly lower for the group treated with PUFA (n = 15), compared to placebo group (n = 14) (p < 0,05).

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Learning and behavioral disabilities (hyperactivity, slow learning, emotional disturb, emotional deficit)	Colgan, M. et al, 1984[66]	Case-control study	USA	n = 32 | 3-15 years | 31,2 % female	Diagnostic: previously obtained | Symptomatology: Stanford-Binet IQ test (cognitive function); Behavior and reading scales (unspecified)	IN PEDIATRIC AGE: individually designed vitamin and mineral supplement + modified diet to reduce sugars, refined foods, and toxic metals contamination	n = 32 (100 %)	---	There was a significant difference in IQ scores in the follow-up of 19 weeks and in reading improvement in the follow-up of 20 weeks, between supplemented group (n = 16) and control group (n = 16) ($p < 0.05$).
Smith-Lemli-Opitz syndrome	Sikora, D. M. et al., 2004[75]	Open trial (6 years follow-up)	USA	n = 14 | 1 month - 13 years, 4 months | 64.3 % female	Diagnostic: previously obtained | Symptomatology: Bayley Scales of Infant Development; Vineland Adaptive Behavior Scales; Peabody Developmental Motor Scales	IN PEDIATRIC AGE: cholesterol supplementation with egg yolks (approximately 18 to 60 mg/kg/d cholesterol, depending on age)	n = 14 (100 %)	---	There were no statistically significant differences between cholesterol supplementation and this syndrome symptoms, at the end of the follow-up ($p > 0.05$).