The Role of Micronutrients in the Prevention and Management of Neurodevelopmental Disorders: A Systematic Review

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ABSTRACT

The prevalence of various neurodevelopmental disorders (NDs) in children continue to progress along a world that is increasingly advancing in research, technology and record keeping. The usual long-term nature of these disorders causes many caregivers to use complementary and alternative medicine (CAM) to help improve the lives of affected children or to prevent the condition from occurring. Micronutrients are among the commonly used CAM in many instances. The objective was to review the role that micronutrients play in the prevention and management of NDs. A search for eligible studies published overtime up to January 2023 was conducted on PUBMED, semantic scholar, TandFonline, and World Health Organisation's International Clinical Trials Registry. The search yielded 2,362 studies, however, 145 reports were included in the review. Serum levels of micronutrients were found to be significantly lower in children with Autism Spectrum Disorder (ASD) and Attention Deficit Hyperactivity Disorder (ADHD) compared to Typically Developing (TD) children. Also, micronutrient usage was associated with perceived improvement in ASD and ADHD symptoms with maternal prenatal intakes and levels of micronutrients lowering the odds of ASD in offspring. Appropriate use of micronutrients in the management of NDs may decrease the severity of these conditions. Additionally, improving maternal serum levels of micronutrients before and during pregnancy may potentially reduce the risk of ASD.

Keywords: Micronutrients, nutrition, neurodevelopmental disorders, autism, Attention Deficit Hyperactivity Disorder, children

Introduction

Neurodevelopmental disorders (NDs) are a group of conditions with onset in the developmental period of a child characterized by developmental deficits that produce impairments of personal, social, academic, or occupational function (APA,2013). These deficits vary among affected people, ranging from very specific learning limitations or control of executive functions to global impairment of social skills or intelligence. The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) describes NDs under six broad categories: Intellectual Disability, Communication Disorders, Autism Spectrum Disorder, Attention Deficit Hyperactivity Disorder, Specific Learning Disorder, and Neurodevelopment motor disorders. These NDs may co-present in individuals and their prevalence range from 9 to 18 percent (Arora et al., 2018; Bosch et al., 2021; Tatishvili et al., 2017).

Genetic disorders (Fragile X syndrome); medical conditions (cerebral palsy and epilepsy); environmental factors (nutrition, perinatal exposures to environmental toxicants(Banerjee et al., 2007; Rossignol et al., 2014), birth by caesarian section(Zhang et al., 2019), perinatal hypoxia, respiratory stress(Arora et al., 2018; Carlsson et al., 2021), diverse maternal inflammatory states during pregnancy(Han et al., 2021), transient income decline during childhood); and biological factors (advanced paternal age, low birth weight, and birth defects)

(Carlsson et al., 2021) have been associated with the risk of NDs .

Due to the stress involved in caring for children with NDs, caregivers continue to explore other measures in an attempt to manage this condition. Hence, Complementary and Alternative Medicine (CAM) is steadily gaining popularity among this population. Multivitamins, vitamin C, vitamin D and minerals are among the most used CAM products among children with neurologic conditions and NDs (Galicia-Connolly et al., 2014; Trudeau et al., 2019; Wilson et al., 2005). Undoubtedly, health workers' ability to provide information that is evidence-based to families that are considering CAM for prevention or treatment of NDs, will prove to be timely and resource saving.

No published systematic review on this topic in whole or in parts exist except a few that has focused on the role of single micronutrients in the treatment of a specific ND(Granero et al., 2021; Hoxha et al., 2021). Hence this review examines the role micronutrients play in the prevention and management of NDs.

METHODS

Eligibility Criteria

All forms of experimental and non-experimental studies about children that relate one or more ND to one or more micronutrients were included in this review. Studies published in English and had reported on children up to 18 years of age were eligible for inclusion. Studies on animal subjects and the effect of toxic metals were excluded.

Information Sources

Using PUBMED, Semantic scholar, Tandfonline, the WHO International Clinical Trials Registry Platform (ICTRP), and Cochrane CENTRAL, a search was made for published and gray materials concerning the subject being reviewed.

Search Strategy

As required for a good search strategy, a review protocol was developed (Aromataris & Riitano, 2014). The primary outcomes for the search were: the effectiveness of micronutrients in treating NDs, the biological levels of micronutrients in children with NDs and the risk associated with levels and usage of micronutrients in relation to NDs. Using various sentences that included MeSH terms like; micronutrients, minerals, vitamins, diet, treatment, prevention, management, neurodevelopmental disorders and children, the search for published materials was made. A Boolean search was also made on the ICTRP for gray material. Filters were applied to include only articles with full free texts that were published up to 15th January 2023 and exclude commentaries, books and documents.

Study Selection Process

The principal author scanned through all abstracts of studies obtained from all aforementioned search engines. When there was uncertainty about an abstract, the full version was sought for. Also, full versions of studies that did not have abstracts were sought for and scanned for relevance. The co-authors double-checked to ensure that all articles qualified for inclusion in accordance to the PRISMA study selection guidelines(Matthew J Page et al., 2020).

Data Collection Process

Relevant information from the different studies were identified and tabulated by the principal author and co-authors double-checked the entries. Similar research designs were entered in succession and where available, *P*-values, confidence intervals and standard deviations were added to the extraction table.

Data Items

Outcomes included in the data collection were the type of study, population studied, type of NDs studied, kind of micronutrient studied, and results of relevance to the review.

RESULTS

Study selection using the PRISMA flow diagram

Using the PRISMA flow diagram, the study selection process has been explained below in Fig.1.

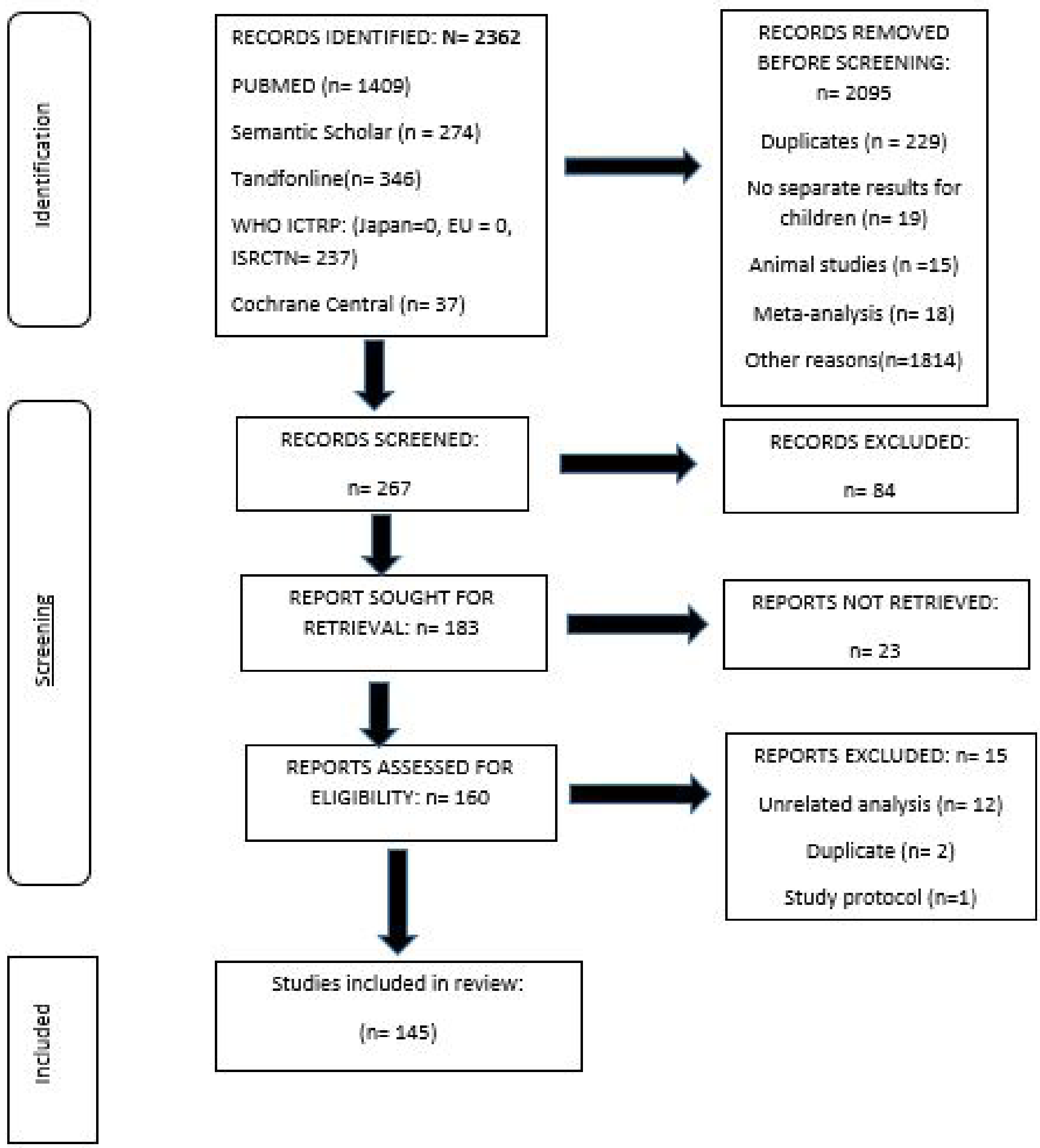

FIG.1

Study Characteristics

Table 1: The Use of Micronutrients in the Management of ND Symptoms.

Study Type and Area	Age (years)	Number of Subjects	Micronutrient Studied	Outcome	Reference
Studies on Autism Spectrum Disorders (ASD)					
[1]CR, UK	4	1 boy	Vitamin D and calcium	Supplementation with Ca and Vitamin D resulted in hypercalcaemia and hypervitaminosis D.	(Boyd & Moodambail, 2016)
CR, China	2	1 girl	Vitamin D	Six months supplementation with vitamin D3 didn't improve autism rating.	(Feng et al., 2020)
CR, India	5	1boy	B6, B9, B12	[2]CARS score decreased to 32 after treatment with the B vitamins.	(Gowda & Srinivasan, 2022)
[3]CS survey, USA	<17	1286(966 children)	Vitamin and mineral supplements	The uses of any B12, Calcium, Magnesium, Zinc, Vitamin D, or a multivitamin specifically formulated for ASD were significantly related to perceived positive improvement in ASD symptoms[$p \leq 0.01$].	(Adams et al., 2021)
CS Survey, USA	9.9±4.1	157 primary caregivers	Multivitamin, B12 and Zn	On a scale of 1-5, the average parental rating of the effectiveness of multivitamin was 3.65, methyl B12 injection was 4.01 and Zn was 3.96.	(Hopf et al., 2016)
Retrospective open-label [4]CaS,USA	4-11	19	Fe	The majority of children with ASD, [5]RLS and serum ferritin <30 μg/L had improvement on the [6]CGI scale and significantly better serum iron parameters after a single IV [7]FCM infusion.	(DelRosso et al., 2022)

1 Case Report
2 Childhood Autism Rating Scale
3 Cross Sectional
4 Case Series
5 Restless Leg Symptoms
6 Clinical Global Impression
7 Ferric Carboxymaltose

Study Type and Area	Age (years)	Number of Subjects	Micronutrient Studied	Outcome	Reference
[8]RDBPCT, USA	5-16	53(26cases)	Combined Vitamins (8) and minerals (14)	For the [9]PGI-R Average Change, the supplement group had a significantly greater improvement than the placebo group (p= 0.003).	(Adams et al., 2011)
[10]OLT, China	1-3	102 cases (30 routine treatment + 37[11]ESDM + 35 ESDM & Vit D3)	Vitamin D	ESDM + Vit D3 group, showed the highest (but statistically insignificant across groups) improvement (p< 0.01) on the [12]CARS and [13]ABC scores.	(Feng et al., 2019)
Two-arm RDBPCT, USA.	3-14	48(23 cases)	[14]Vitamin B_9	Verbal communication improvement, was significantly greater in treatment group compared to placebo group (Cohen's d=0.70).	(Frye et al., 2018)
[15]RCT, Russia	3-14	99(74 cases)	I	Iodine-Bromine baths decreased stress system indicators significantly (p<0.01) in cases with hyperactivity.	(Golubova & Nuvoli, 2022)
[16]RDBPCT, USA	3-7	57	Vitamin B_{12}	After 8 weeks, the [17]CGI-I score was statistically significantly better in the methyl B12 group than in the placebo group (p=0.005).	(Hendren et al., 2016)
[18]OLT, USA	2-7	82(40 cases)	Vitamins B_{12} (Methyl cobalamin) and B9	There were significant increases in the transmethylation metabolites and glutathione concentrations (P< 0.001) after 3 months treatment.	(James et al., 2009)

8 Randomised Double-Blind Placebo-Controlled Trial
9 Parental Global Impression- Revised
10 Open-Label Trial
11 Early Start Denver Model
12 Childhood Autism Rating Scale
13 Autism Behaviour Checklist
14 Folinic Acid
15 Randomised Controlled Trial
16 Randomised Double-Blind Placebo-Controlled Trial
17 Clinical Global Impressions
18 Open-Label Trial

Study Type and Area	Age (years)	Number of Subjects	Micronutrient Studied	Outcome	Reference
Intervention study, Poland	3-16	236 cases	Vitamin B and Magnesium	Supplementation with vitamins B and magnesium greatly impacted tryptophan (an amino acid involved in sleep disorder in ASD) levels ($p < 0.05$).	(Kałużna-Czaplińska et al., 2017)
Single-blind non-randomized intervention pilot study, China	1-6	64	Vitamin A	The scores of ABC, CARS and [19]SRS scales showed no significant differences ($P > 0.05$) in all subjects after 6 months of intervention.	(Liu et al., 2017)
RDBPCT, New Zealand	2-8	67 (Intervention group=51)	Vitamin D	With all children included, Vitamin D had no effect on behavioural outcomes. When only children with elevated IL-1β at baseline were included, Vitamin D produced a greater improvement in SRS-awareness ($P = 0.01$).	(Mazahery et al., 2020)
An intervention study, France	1-10	66 (33 cases)	Magnesium and vitamin B_6	The Mg-B6 regimen led to improvement in ASD symptoms in 23/33 children ($p < 0.0001$).	Mousain-Bosc et al., 2006)
An intervention study, Germany	2-12	25 cases	[20]Vitamin B_9	[21]CSF [22]5MTHF was low in 23 patients. Oral B9 supplementation led to partial or complete clinical recovery.	(Ramaekers et al., 2007)
[23]OLT, China	3-6	66 (22 matched controls)	Vitamin B_9	800µg folic acid daily for 3 months improved autism symptoms($p < 0.05$).	(Sun et al., 2016)
Studies on Attention Deficit Hyperactivity Disorder (ADHD)					

19 Social Responsiveness Scale
20 Folinic Acid
21 Cerebrospinal Fluid
22 5-methyltetrahydrofolate
23 Open-Label Trial

Study Type and Area	Age (years)	Number of Subjects	Micronutrient Studied	Outcome	Reference
[24]RDBPCT, USA	6-14	52(24 placebo-matched controls)	Zinc	Zinc did not improve ADHD symptoms except in parent-rated inattention(d=-0.31).	(Arnold et al., 2011)
Open label, (reversal design), New Zealand	8-12	18 cases	Combined minerals and multivitamins	Clinically and statistically significant change in ADHD symptoms between the intervention and withdrawal phases (d=1.2–2.2).	(Gordon et al., 2015)
RDBPCT, Iran	6-12	66(intervention arm=33)	Magnesium and Vitamin D	The intervention group had significant reduction in several ADHD scores ($p \leq 0.007$) compared to placebo group.	(Hemamy et al., 2021)
[25]RDBPCT, USA	6-12	135(81cases)	All vitamins & known essential minerals	No significant between-group differences were found on the parent-rated [26]CASI-5 composite score (p = .70); On individual CASI-5 subscales, a DMDD trend favoured micronutrients (−0.42) over placebo (−0.22) in symptom reduction (p = .09).	(Johnstone et al., 2022)
RDBPCT, Iran	6-12	86(42cases)	Vitamin D	No significant reduction in 8-isoprostan as an oxidative stress marker in both the treatment and placebo groups ($P < 0.05$)	(Mohammadzadeh Honarvar et al., 2022)
[27]RCT, Thailand	[28]N/A	52(26cases)	Fe	Total parents' Vanderbilt ADHD symptom scores showed a significant improvement between the groups ($p = 0.037$) after treatment with methylphenidate and iron.	(Pongpitakdamrong et al., 2022)
RCT, Iran	6-15	120	Vitamin D	Significantly lower ADHD mean scores in the group treated with neurofeedback combined with Vit.D.	(Rahmani et al., 2022)

24 Randomised Double-Blind Placebo-Controlled Trial
25 Randomised Double-Blind Placebo-Controlled Trial
26 Child and Adolescent Symptom Inventory-5
27 Randomised Controlled Trial
28 Not Available

Study Type and Area	Age (years)	Number of Subjects	Micronutrient Studied	Outcome	Reference
RDBPCT, New Zealand	7-12	93(Treatment arm=47).	Minerals and multivitamins	Significant between-group differences favouring micronutrient treatment on the [29]CGI-Improvement (ES=0.46).	(Rucklidge et al., 2018)
RDBPCT, Iran	6-12	86(42cases)	Vitamin D	Three months supplementation with Vit.D did not have significant effect on inflammatory cytokines (IL-6 and TNF-α).	(Samadi et al., 2022)
RCT, New Zealand	7-12	17(Treatment arm=10)	Minerals and vitamins	A significant difference in the change of observed [30]OTU between the treatment and placebo groups (p =0.05).	(Stevens et al., 2019)
Database analysis, Canada	7-8	120 children with bipolar disorder (24% ADHD)	36-ingredient micronutrient formula (EMPowerplus)	A 40% decline in ADHD symptoms observed (ES= 0.62).	(Rucklidge et al., 2010)
Studies on Intellectual Disability					
[31]CaS, Saudi Arabia	4&5	2 siblings	Vitamin B9	Daily dosing of folinic acid caused seizures to stop and improved neurological functioning in both cases.	(Al-Baradie & Chaudhary, 2014)
[32]RDBPCT, USA	5-8	2 sets of identical twins	Vitamin B9	No statistically significant changes in the developmental testing scores between groups after 1-year treatment with folic acid.	(Han et al., 2019)
Exploratory study (double blind experiment), UK	5-15	16(group1=5, group2=11)	8 minerals and 11 vitamins	During phase1 and phase 2, the supplement group significantly increased their average IQ by 5.0-9.6($p < 0.05$) and at least 10.2($P < 0.001$) respectively, but the placebo group showed negligible change.	(Harrell et al., 1981)

29 Clinical Global Impression

30 Operational Taxonomic Units

31 Case Series

32 Randomised Double-Blind Placebo-Controlled Trial

Study Type and Area	Age (years)	Number of Subjects	Micronutrient Studied	Outcome	Reference
RDBPCT, USA.	2- 5	60(31treatment)	Choline	The treatment effect on [33]EI items recalled was significant in the younger participants (≤4.0yrs). An inverse relation between choline dose and memory improvement (p= 0.041) was observed.	(Wozniak et al., 2015)
Studies on Specific Learning Disorders					
CaS, UK.	7-11	3 cases	Vitamin B_6	Intellectual performance overtime did not increase, and it did not differ among all cases.	(Rankin et al., 2007)
Placebo-controlled double-blind study, Canada	7-14	20(10treatment)	Vitamins B_1, B_3, B_5 and C	No significant between group differences were found in the test scores after 6 months	(Kershner et al., 1977)
Studies on Neurodevelopment Motor Disorders					
[34]CS-c, UK	5-7	76(42 Tourette syndrome cases +34 controls)	Vitamins and mineral supplements	Multivitamin users (n=6) didn't report any notable changes, but magnesium users (n=3) reported improved vocal tics	(Smith & Ludlow, 2021).
[35]OLT, Italy	4-17	34(17cases)	Vit.B6	Combined L-Theanine and vitamin B6 was significantly more effective than psychoeducation in reducing tics(p≤0.05).	(Rizzo et al., 2022)

33 Elicited Imitation

34 Cross – Sectional Comparative

35 Open-Label Trial

Table 2: Micronutrients levels and the Prevention of NDs.

Studies on the Levels of Micronutrients in ASD					
[36]CR, Australia	12	1 boy	Vitamin A, B_9 and Iron	Low vitamin A, haemoglobin and folate levels observed.	(Chiu & Watson, 2015)
CR, Sweden	7	1 boy	Vitamin A	Xerophthalmia with retinol <0.2μmol/l	(Enekvint et al., 2021)
CR, Canada	6	1 boy	Vitamin C, D, and Iron	Low serum ascorbic acid, Fe , and 5-(OH)D observed	(Erdle et al., 2017)
CR, UK	4	1 case	Vitamins A and D	Hypercarotenaemia and low Vitamin D level observed.	(Keown et al., 2014)
CR, Canada	10	1 boy	Vitamins C, A, D and Zinc	Abnormally low ascorbic acid level(<5μmol/l) and low levels of Vitamin A, D, and zinc observed.	(Kinlin et al., 2018)
CR, Italy	3	1 girl	Vitamin C, D and B_9	Low Vitamin C (below limit of quantification), vitamin D and folate levels.	(Liuzzo Scorpo et al., 2021)
CR, Italy	4	1 boy	Vitamin C	Low serum vitamin C and haemoglobin observed.	(Saavedra et al., 2018)
[37]CaS, USA	5-17	6	Vitamin A	All subjects had a barely detectable Vitamin A level (<10 mcg/dL)	(Godfrey et al., 2022)
[38]CS-c, Saudi Arabia	3-12	82(30 matched controls)	Vitamin E	Cases had lower vitamin E concentrations that correlated with the severity of the social and cognitive impairment measures.	(Alabdali et al., 2014)

36 Case Report
37 Case Series
38 Cross-Sectional Comparative

[39]CS-c, Canada	<18	34(27 cases)	Copper and Zinc	Cases had lower prenatal($p<0.001$) and postnatal ($p<0.05$) Cu, and lower Copper-to-Zinc ratio compared to controls. Language and communication scores were positively related to prenatal Cu exposure and Cu/Zn ratio ($p<0.05$).	(Frye et al., 2020)
CS-c, USA	8-14	37(18 cases)	Vitamin D, Ca	Serum levels for Ca and vitamin D did not differ between groups.	(Neumeyer et al., 2013)
[40]CS, Pakistan	5-11	61 cases	Vitamin D	85% had below normal 25(OH)D levels.	(Cheema et al., 2016)
Retrospective chart review, Canada	1-10	96 cases	Iron	Lower ferritin values correlated with higher communication scores ($p= 0.005$)	(Dosman et al., 2006)
CS, USA	2-11	222 cases	Iron	Only 8% had Serum Ferritin (SF) <12μg/L and 1% had Iron deficiency.	(Reynolds et al., 2012)
Multicentre survey, China	2-7	2600(1321 cases)	Vitamin D	Serum 25(OH)D levels were significantly lower in cases than in healthy controls and were associated with the presence or absence of ASD.	(Qi et al., 2022)
CS, Japan	≤15	1967 cases	Zn, Mg, Ca, Fe, Cr, Mn, Cu, Co	Scalp hair analysis showed Zn, Mg and Ca deficiencies in 29.7%,17.6% and 5.8% cases respectively. Incidence rate less than 2% was recorded for the other minerals.	(Yasuda et al., 2013)

39 Cross-Sectional Comparative

40 Cross-Sectional

CS-c, China	N/A	589(269cases)	Vit.D	Cases had significantly lower levels of serum vitamin D and a significantly higher rate of vitamin D deficiency (< 20 ng/ml) compared to healthy controls (67.7% vs 34.1%).	(Zhang et al., 2022)
CS-c, China	2-6	180(120cases)	Vitamins A, B, C	Vitamins B, A and C faecal concentrations were reduced (p<0.05). B6 negatively correlated with partial subscales. Vitamin A positively correlated with neurodevelopment scores.	(J. Zhu et al., 2022)
CS-c, Omani	3-4	80(40 matched controls)	Vitamin B9 and B12	Significantly lower serum folate and B12 levels observed in cases compared to controls (p<0.05).	(Ali et al., 2011)
CS-c, Iran	5-12	62(31 cases)	Vitamin D	Average serum 25(OH)D level in the cases was significantly lower (*P* >0.001) than the control group	(Arastoo et al., 2018)
CS-c, Czech Republic	4-7	85(40 matched controls)	Vitamin D	No significant difference in vitamin D level was observed between groups.	(Bičíková et al., 2019)
CS-c, India	6-14	20(10 cases)	Zinc	Lower but insignificant mean concentration of salivary zinc in cases compared to controls.	(Deshpande et al., 2019)
CS-c, China		226(117 cases)	Vitamin D	Serum level of 25(OH)D was significantly lower in cases than in healthy controls (P<0.01).	(Du et al., 2015)
Exploratory study, Italy	3-8	80(40 matched controls)	Vitamin C and B6	Significantly higher vitamin C levels (p<0.001) and lower levels of active form of vitamin B6 (P<0.05) in cases.	(Gevi et al., 2020)
CS-c, Japan	3-9	97(58 matched controls)	Vitamin E	Higher but insignificant α-tocopherol levels in ASD cases (p= 0.967) than control.	(Hirayama et al., 2020)
CS-c, USA	2-7	102(68 cases).	Iron	No significant differences in mean serum ferritin levels between groups.	(Lane et al., 2015)

CS-c, USA	4-8	89(49 cases)	Vitamin D	No significant group differences of 25(OH)D levels were observed (*p* =0.4).	(Molloy et al., 2010)
[41]CS-c, Saudi Arabia	5-12	80(30 matched controls)	Vitamin D	Cases had significantly lower serum levels of 25(OH)D, (*P*< 0.001), which had significant negative correlations with [42]CARS (P< 0.001)	(Mostafa & Al-Ayadhi, 2012)
CS-c, Saudi Arabia	3-10	200(100cases)	Vitamin D	Significantly lowered [43]OR for Autism was observed for children consuming a Vitamin-D rich diet (OR=0.23, 95% CI=0.11-0.46)	(Oommen et al., 2018)
CS-c, Italy	<18	90(54 cases)	Vitamin D	Mean level of 25(OH)D was significantly lower in cases (*p*= 0.014) and it had an association with ASD (p= 0.006)	(Petruzzelli et al., 2020)
CS-c, Jamaica	2-8	218(109 matched controls)	Manganese	No significant association was found between Blood Manganese Concentration and ASD, (P =0.29).	(Rahbar et al., 2014)
Retrospective and CS-c, Turkey	3-18	Phase I: n=1521 Phase II: n=200 (100 cases)	Vitamin D Calcium and phosphorus	Mean vitamin D level was significantly lower in cases than in controls (P=0.037), Ca was not significantly different between groups, but P was significantly higher among the cases (p=0.015).	(Şengenç et al., 2020)

41 Cross-Sectional Comparative
42 Childhood Autism Rating Scale
43 Odds Ratio

CS-c, Russia	1-9	90(60 cases)	12 minerals	Hair Ca and Se levels were significantly lower in cases (p=0.002 and p=0.004 respectively). No significant difference in serum Ca between groups. Hair Zn level was insignificantly lower among cases. Serum V and Mg were significantly higher among cases.	(Tinkov et al., 2019)
Multicenter CS-c, China.	2-7	2058(1038 matched controls)	Zinc, magnesium and copper	Serum Mg, Cu, and Zn levels in cases were significantly lower than in controls ($P< 0.05$). Mg and Zn levels inversely correlated with the total and communication ability scores.	(Zhang et al., 2021)
CCS, China	N/A	183(92cases)	Ca, K, Mg, Na, Mn, Se, Co, Mo, Cu, Zn, Fe	Ca, K, and Mg were significantly higher in the cases than in the controls. Zn and Cu were significantly lower in cases	(Ma et al., 2022)
[44]CCS, Malaysia	3-6	155(81 cases)	Ca, Mg, Zn and Fe +	Urinary Mg, Zn, Fe, and Ca were significantly lower ($p<0.05$) in both groups. The odds of ASD reduced significantly by 5.0% and 23.0% with an increment of every 1.0µg/dL urinary Zn and Fe, respectively.	(Abd Wahil et al., 2022)

44 Case-control Study

CCS, Qatar	<8	616(308 cases)	Vitamin D and Iron + Mg, K, Ca and P	Significantly lower serum iron levels in cases than in controls (p =0.003). Significantly higher Vitamin D deficiency among cases (p= 0.004). Significantly higher levels of the other minerals in controls compared to cases (p< 0.001).	(Bener et al., 2017)
CoS, Poland.	6-10	287	Selenium	The presence of ASD was associated with lower serum and toenail selenium (p< 0.001).	(Błażewicz et al., 2020)
CoS, UK	<1	6644 pregnant women + 7013 children	Iodine	No association between I:Creatinine or Urinary Iodine Concentration and ASD risk in children aged 8–12 years (p= 0·3).	(Cromie et al., 2020)
CoS, China	3	1550(310cases)	Vitamin D	The median 25(OH)D3 level was significantly lower in children with ASD compared to controls (p< 0.0001). Neonatal vitamin D status was significantly associated with ASD risk and intellectual disability	(Wu et al., 2018)
Studies on Maternal micronutrient intake/serum levels and prevention of ASD					
CCS, Sweden	4-17	200(100 cases)	Vitamin B9 and D	Positive association between higher maternal serum folate concentrations and increased ASD occurrence (OR per 1 SD increase: 1.70, 95% CI 1.22–2.37). No association between maternal Vitamin D3 level and offspring autism occurrence.	(Egorova et al., 2020)

CCS, USA	2-5	606(346 cases)	Vitamin B9	High [45]FA intake (>800µg) in the first pregnancy month was associated with decreased ASD despite exposure to air pollutants, during the first trimester (*P*-interaction = 0.04).	(Goodrich et al., 2018)
Population – based [46]CCS, USA	2-5	566(288 cases)	Prenatal vitamins	Prenatal vitamins use 3 months before pregnancy through to the first month was associated with lower risk for autism (unweighted OR = 0.62 [95% CI = 0.42–0.93])	(Schmidt et al., 2011)
CCS, USA	2-5	724 cases and controls	Vitamin D	No association between a 25nmol/L increase in maternal 25(OH)D and ASD was observed (OR=0.97, CI: 0.87, 1.08).	(Schmidt, Niu, et al., 2019)
CCS, USA	2-5	806(466 cases)	Vitamin B9	ASD was increased in association with < 800µg of FA and any indoor pesticide exposure compared to low FA [OR= 1.2 (95% CI: 0.7, 2.2)] or indoor pesticides [OR = 1.7 (95% CI: 1.1, 2.8)] alone.	(Schmidt et al., 2017)
CCS, USA	2-5	866(520 cases)	Iron	The highest category of maternal iron intake (≥86 mg/day) during the index period was associated with significantly reduced risk of ASD in the child (OR= 0.49, 95% CI: 0.29, 0.82).	(Schmidt et al., 2014)
CCS, USA	2-5	837(429 cases)	Vitamin B9	A mean daily FA intake of ≥600µg during pregnancy month1 was associated with reduced ASD risk (aOR: 0.62; 95% CI: 0.42, 0.92).	(Schmidt et al., 2012)

45 Folic Acid

46 Case-Control Study

ISSN: 2821-9007 (Online)

Nested CCS, Finland	N/A	3116(1558 controls)	Vitamin D	The increased risk of ASD was associated with deficient (aOR 1.44, 95% CI 1.15–1.81) and insufficient maternal 25(OH)D levels (aOR 1.26, 95% CI 1.04–1.52,) compared with sufficient levels.	(Sourander, Upadhyaya, et al., 2021)
Nested CCS, USA	2-5	516(296 cases)	Vitamin B9	Children with pesticide exposure and low maternal FA intake were at least twice as likely to have ASD than those with no exposure and high maternal FA intake.	(Barrett, 2017)
CCS, Sweden	<1	Maternal sample = (449 cases + 574 controls) Neonatal sample = (1399 cases + 1607 controls)	Vitamin D	In adjusted models, compared with neonates with 25(OH)D ≥50nmol/L, those with 25(OH)D <25nmol/L had 1.33 times higher odds of ASD. Children with both maternal 25OHD and neonatal 25OHD below the median had 1.75 times the odds of ASD compared with children with maternal and neonatal 25OHD both below the median.	(B. K. Lee et al., 2021)
Population-based, prospective [47]CoS, Norway	<1	109,000	Vitamin B9	In children whose mothers took folic acid, 0.10% had ASD, compared with 0.21% in those unexposed to folic acid. [aOR =0.61,95% CI:0.41–0.90).	(Berry, 2013)
Observational prospective CoS, Sweden	4-15	273,107 mother-child pairs	Multivitamin, Vitamin B9 and iron	Maternal multivitamin use with or without additional iron or folic acid, or both was associated with lower odds of offspring ASD with intellectual disability (OR 0.69, 95%CI: 0.57-0.84).	(DeVilbiss et al., 2017)

47 Cohort Study

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CoS, Israel	<1	45,300 mother-child pairs	Multivitamin and Vitamin B9	Maternal exposures to folic acid and/or multivitamin supplements before or after pregnancy were both significantly associated with a lower likelihood of offspring ASD compared with no exposures before or after pregnancy. Before:(RR, 0.39; 95% CI: 0.30-0.50); After:(RR, 0.27; 95% CI: 0.22-0.33)	(Levine et al., 2018)
Prospective CoS, Canada	3-4	610 mother – child pairs	Vitamin B9	Folic Acid supplementation during pregnancy consistently and significantly attenuated the positive associations between gestational urinary phthalate concentrations and greater risk of overall social impairment.	(Oulhote et al., 2020)
Prospective CoS, USA	<1	1257 mother – child pairs	Vitamin B9, B12 and multivitamins	There was a "U" shaped relationship between maternal multivitamin supplementation frequency and ASD risk. Very high levels of maternal plasma folate and B12 at birth had 2.5 times increased risk of ASD compared to folate levels in the middle 80th percentile[95%CI;1.3-4.6(Folate); 1.4-4.5(B12)].	(Raghavan et al., 2018)
Prospective CoS, Norway	3-7	85176 (61042 mothers exposed)	Vitamin B9	Of the children whose mothers took folic acid from 6 weeks before to 6 weeks after conception, 0.10% had autistic disorder, compared with (0.21%) of the children whose mothers did not (aOR 0.61, 95% CI 0.41 to 0.90).	(Schmidt, 2013)

[48]CoS, UK	N/A	5015 mother-baby pairs	Vitamin D	No significant association between maternal serum 25-hydroxyvitamin D during pregnancy and any offspring autism-associated outcome was found (aOR=0.98, 95% CI=0.90–1.06)	(Madley-Dowd et al., 2022)
Nationwide prospective CoS, Japan	3	96,931mother-child pairs	B9	No association between prenatal folic acid supplementation and ASD in offspring(aOR, 1.189; 95%CI, 0.819-1.727).	(Nishigori et al., 2022)
Prospective CoS, USA	2-5	241 younger siblings of ASD children + mothers	Prenatal vitamins	Prenatal vitamins during the first month of pregnancy is associated with lesser offspring ASD diagnosis (aRR= 0.50; 95% CI, 0.30-0.81) but not a non-[49]TD 36-month outcome (aRR, 1.14; 95% CI, 0.75-1.75) compared with no prenatal vitamins exposed mothers.	(Schmidt, Iosif, et al., 2019)
[50]OLT, USA	3	19 pairs	Vitamin D	5% siblings born to mothers given vitamin D developed autism in contrast to the known recurrence rate of approximately 20%.	(Stubbs et al., 2016)
Studies on Levels of Micronutrients in ADHD					
[51]CS, USA	5-10	48	Zinc and Magnesium	Normal serum Mg levels were observed. Serum Zn correlated at r = -0.45 (p= 0.004) with parent-teacher-rated inattention.	(Arnold et al., 2005)

48 Cohort Study
49 Typically Developing
50 Open-Label Trial
51 Cross-Sectional

CS, Turkey	6-15	89	Iodine	Significant association was found between urinary iodine levels and hyperactivity section of [52]CTRS ($p < 0.05$).	(Kanık Yüksek et al., 2016)
Multi-centre CS, Turkey	5-12	100 cases	Iron and Vitamin B12	[53]CPRS total scores were not significantly associated with the Hb and ferritin or vitamin B12 levels ($p > 0.05$).	(Unal et al., 2019)
Secondary data analysis from a multiphase, [54]RDBPCT, USA.	6-14	52	Iron	87% of the sample had a low ferritin concentration at baseline. Serum ferritin concentration inversely correlated with ADHD scores ($p < 0.05$).	(Calarge et al., 2016)
[55]CS-c, Egypt		100(75cases)	Zinc and iron	Serum ferritin level in cases was significantly lower compared to the control. Serum Zn was significantly higher in the ADHD compared to the control group.	(Abd El Naby & Naguib, 2018)
CS-c, Egypt	6-12	103(41 cases)	Iron	There were no significant differences in ADHD symptoms or ADHD index subscale scores between children with serum ferritin levels <30ng/mL and those ≥30ng/mL ($p > 0.05$).	(Abou-Khadra et al., 2013)
CS-c, USA	8-18	49(22 cases)	Iron	No significant differences ($p > 0.05$) in brain iron measures between control subjects and ADHD patients.	(Adisetiyo et al., 2014)

52 Corner's Teacher Rating Scale

53 Conner's Parents Rating Scale

54 Randomised Double-Blind Placebo-Controlled Trial

55 Cross-Sectional Comparative

CS-c, USA	8-18	59(30cases)	Iron	Youth with ADHD may have less prominent age-related brain iron increases than that seen in typical development, which long-term use of psychostimulant medications may compensate.	(Adisetiyo et al., 2019)
CS-c, China	6-14	102 (51 cases)	Fe	Several brain regions were iron deficient. The left anterior cingulum showed positive correlation with the symptom severity ($r = 0.326$, $p < 0.05$).	(Chen et al., 2022)
CS-c, Turkey	6-7	70(40 cases)	Vitamin B9	No statistical difference ($p=0.055$) in blood folic acid levels between groups.	(Gokcen et al., 2011)
CS-c, USA	5-18	108(82 cases)	Iron	No significant differences in ferritin levels for those with and without ADHD.	(Gottfried et al., 2013)
CS-c, USA	7-12	34(17 cases)	Vitamin D	No significant differences between children with and without ADHD for vitamin D.	(Holton et al., 2019)
[56]CS-c, Egypt	5-15	83(58 cases)	Zn, Fe, Mg and Cu	Serum zinc, ferritin and magnesium levels were significantly lower in cases than controls ($p<0.05$) Copper levels were not significantly different.	(Mahmoud et al., 2011)
CS-c, Brazil	6-15	62(41cases)	Iron	No significant correlation between dimensional measures of ADHD symptoms and ferritin levels was found.	(Menegassi et al., 2010)

56 Cross-Sectional Comparative

CS-c, Turkey	11-14	118 cases	Zinc and Iron	[57]CPRS Total score was significantly related with serum zinc level. CPRS Hyperactivity score was associated both with zinc and ferritin levels.	(Oner et al., 2010)
CS-c in China	5-16	102(53cases)	Fe	The brain total iron content of children with ADHD was lower than that of healthy children ($p < .05$)	(Tang et al., 2022)
CS-c, China	6-14	592(296 cases)	Zn, P, Se, Ca, Vitamin B2	A nutrient pattern rich in zinc, phosphorus, selenium, calcium, and riboflavin was inversely associated with ADHD (p=0.014). Blood zinc was negatively related to ADHD (p=0.003).	(Zhou et al., 2016)
[58]CCS, Turkey	6-15	60(30 matched controls)	Vitamins B6, B9 and B12	Pyridoxine, folate, and vitamin B12 were significantly lower in the cases compared to the control group (p<0.05) No correlation between age, intelligence level and pyridoxine, folate and vitamin B12 levels except positive correlation between intelligence level and vitamin B12 (p<0.05).	(Altun et al., 2018)
CCS, Sweden	5-17	404(202 matched controls)	Vitamin D	No significant differences in cord blood vitamin D concentration were found between cases and controls (p=0.43). No linear association between ADHD and vitamin D levels (OR: 0.99, 95% CI:0.97–1.02).	(Gustafsson et al., 2015)

57 Conners's Parent Rating Scale
58 Case-Control Study

CCS, Sweden	5-17	332(166 cases)	Selenium and manganese	No associations between cord manganese or selenium concentration and ADHD were observed. Children with selenium concentrations above the 90th percentile had 2.5 times higher odds (95% CI:1.3–5.1) of having ADHD.	(Ode et al., 2015)
Nationwide [59]CoS, Denmark		643,401	Manganese	Exposure to Mn >100μg/L of water at any one time during the first 5yrs of life was associated with a 51% and 20% increased risk of ADHD in females and males respectively.	(Schullehner et al., 2020)
Prospective study, Spain	6-14	60 cases	Iron	About 63% had iron deficiency.	(Soto-Insuga et al., 2013)
RDBPCT, Netherlands	8-18	63(33placebo)	Fe, Zn	No significant correlations between baseline ferritin and zinc serum levels and the baseline ADHD scores(p>0.05)	(Rosenau et al., 2022)
Studies on Maternal micronutrient intake/serum levels and prevention of ADHD					
Nested CCS, Finland	2-14	2052(1026 matched controls)	Vitamin B12	Lower maternal Vitamin B12 levels was not associated with offspring ADHD (aOR 0.97, 95% CI 0.79–1.18).	(Sourander, Silwal, et al., 2021)

59 Cohort Study

Prospective Population-based CoS, Norway	6-13	53,360 mother-child pairs	Iodine	No association between iodine intake from food and risk of child ADHD diagnosis (p= 0.89). No beneficial effects of maternal use of iodine supplements on child ADHD diagnosis or symptom score was found. Iodine supplement use in gestational weeks 0-12 was associated with a ~29% increased risk of ADHD diagnosis (95% CI: 0–67%, p= 0.053)	(Abel et al., 2017)
CoS, USA	6-9	680 mother-child pairs	Vitamin D	No associations between maternal 25(OH)D at 10–18 weeks of gestation and offspring ADHD observed. Associations between maternal vitamin D sufficiency and offspring ADHD observed in the third trimester [OR: 0.47, 95% CI: 0.26–0.84].	(Chu et al., 2022)
CoS, Spain	7	946 mother-child pairs	Fe	Hb levels in the first and third trimester of pregnancy were not related to ADHD risk in children.	(Díaz-López et al., 2022)
Based on Danish National Birth Cohort	7	1026 (642 ADHD)	Vitamin B9 and multivitamin	No association between early folic acid supplementation and ADHD medication prescription. Early multivitamin use in pregnancy was associated with about 21% reduced risk for ADHD medication prescriptions (aHR: 0.79, 95% CI:0.62–0.98)	(Virk et al., 2018)

Studies on Micronutrient levels in ID					
Case series, Egypt	5-17	6 cases	Manganese and Zinc	Mn and Zn levels in blood were either low or very low-normal in all cases due to defective Mn and Zn transport.	(Boycott et al., 2015)
Case report, USA	9	1girl	Iron and vitamins	Pica eating and iron deficiency and anaemia were resolved with iron and multivitamin supplementation.	(Pace & Toyer, 2000)
[60]CS, Poland	Not given	82 cases	Mg, Ca, Cu. Zn and Fe	Fe concentrations in hair was found to be generally lower. Mg, Ca, Cu and Zn levels varied for the different subgroups.	(Józefczuk et al., 2017)
CS, Canada.	3-9	77	Vitamin A	22% had serum carotenoid level above 300μg/ml.	(Patel et al., 1973)
Retrospective review, Korea	7-15	143 cases	Vitamin D	25(OH)D_3 levels were lower in cases than in patients with normal intelligence quotient levels (p=0.03)	(Baek et al., 2014)
Studies on Micronutrient levels and/or their association with SLD					
CS-c, Jordan	3-7	70(35cases)	Mg, Fe, K, Zn	All minerals in hair were similar between groups except Zn that was significantly lower in cases (p<0.05)	(Rashaid et al., 2022)
CS-c, China	[61]MA=9.7±1.3	469(239cases)	Mn	The highest quartile of urinary manganese was found to have a 3.87-fold (95 % CI = 1.39-10.74) elevated dyslexia risk compared with the lowest quartile among the rs27072 mutation carriers.	(K. Zhu et al., 2022)

60 CS- Cross-Sectional
61 Mean Age

[62]CS-c, China	8-11	456(228 cases)	Selenium and other metals	The multivariable-adjusted ORs of dyslexic children were 0.32 (95%CI: 0.13–0.83) for selenium, and 3.31 (95%CI: 1.09–10.05) for argentum. No significant associations were observed for other metals.	(Xue et al., 2020)
National Health Survey, USA	4-11	1,076	Se	Serum Se concentration was lower among children with LD than those without LD (P=0.08). Each 10 ng/mL increment in serum Se concentrations was associated with 31% (OR 0.69, 95% CI 0.51-0.93) lower odds of LD	(Liu et al., 2022)
Nested [63]CCS, Finland.	7-12	3214(1607 matched controls)	Vitamin D	No significant associations between maternal vitamin D and offspring [64]SLD (aOR 0.98, 95% CI 0.82–1.18).	(Arrhenius et al., 2021)
Studies on Micronutrient levels and/or their association with NMD					
CS-c in 9 European countries & Israel	3-16	451(327 cases + 124controls)	Vitamin D	A 10 ng/ml increase in 25(OH) D was associated with higher odds of having [65]CTD (OR 2.08, 95% CI 1.27–3.42,). There was no association between 25(OH)D and tic severity.	(Bond et al., 2022)
CS-c, China	3-14	368(179 cases)	Vitamin D	Serum 25(OH)D level was significantly associated with presence or absence of tic disorder (aOR = 0.89; 95 % CI 0.863–0.921) and was also significantly associated with tic severity (p=0.02).	(Li et al., 2018)

62 CS-c –C ross-Sectional Comparative
63 Case-Control Study
64 Specific Learning Disorders
65 Chronic Tic Disorders

CS-c, China	3-14	276(132 cases)	Vitamin D	Serum 25(OH)D levels were significantly lower in the tic disorder cases than in the control group ($P<0.01$).	(Li et al., 2017)
[66]CS-c, China	6-12	4062cases + controls	Cu, Mg, Mn, Zn, and Fe	There were no significant differences in blood copper, manganese and magnesium levels between children with tic disorders and controls ($P>0.05$). Cases had a significantly decreased blood zinc and iron levels compared to controls ($P<0.05$).	(Liu et al., 2013)
Studies on Micronutrient levels and/or their associations in mixed NDs					
CS-c, Italy	Up to 18	167(93 ASD +74 Other NDs)	Fe	Lower Ferritin in ASD group. Ferritin > 24 ng/mL and [67]MCV showed a significant association with only ASD ($p<0.05$)	(De Giacomo et al., 2022)
CS-c, Turkey	3-18	79(36 ADHD + 18 ASD + 25 controls)	Iron, Vitamins B12 and D	The cases showed significantly lower levels ($p<0.01$) of Iron, vitamin B12 and vitamin D.	(Garipardic et al., 2017)
(Prospective) Multiphase study, USA	5-7	114 cases of NDs	Iron	21% of the sample had serum ferritin level <20μg/L. Ferritin was inversely associated with the severity of disruptive behaviour and positively associated with prosocial behaviour.	(Calarge et al., 2016)
Study based on the EMA population-based [68]CCS, USA	4-9	1189 (563 ASD + 190 ID + 436 controls)	Vitamin D	Lower 25(OH)D was not associated with higher risk of ASD or ID	(Windham et al., 2019)

66 Cross-Sectional Comparative
67 Mean Corpuscular Volume
68 Case-Control Study

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Prospective CoS, USA	N/A	1550 mother-infant dyads	Se	Maternal RBC Se levels were positively associated with child risk of ASD [aOR of 1.49 (95% CI: 1.09, 2.02)] and ADHD. [aOR: 1.29; (95% CI: 1.04, 1.56)] per IQR increase in Se.	(A. S. E. Lee et al., 2021)
3 population –based birth cohorts, (Netherlands, Spain and UK)	Not given	5546 mother-child pairs (ASD and ADHD)	Iodine	Lower Urinary Iodine/Creatinine ratio (<150µg/l) was not associated with ADHD (OR: 1.2; 95% CI: 0.7, 2.2) or with a high autistic-trait score (OR: 0.8; 95% CI: 0.6, 1.1).	(Levie et al., 2020)

Discussion

Autism Spectrum Disorder (ASD) was the most reported category (53.8%) of Neurodevelopmental Disorders (NDs) while Neurodevelopmental Motor Disorders (NMDs) and Specific Learning Disorders (SLDs) were the least reported categories (4..1 % each). More than a third of the extracted documents originated from Europe (41%), followed by the Asia (29%), North America (26%), and Africa (4%). Using the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) classification, studies on all categories of Neurodevelopmental Disorders (NDs) were identified except those on Communication Disorders (CDs). Study outcomes were grouped under two main themes: the use of micronutrients in the management of NDs and micronutrient levels and the prevention of NDs.

The use of Micronutrients in the Management of NDs

In one case report an alternative therapist gave micronutrients to a child with ASD, which led to very elevated levels of calcium and vitamin D (Boyd & Moodambail, 2016). The single micronutrient that was reported most for ASD (9 times) was the B vitamin. All studies on vitamin B, reported significant effectiveness in improving ASD core symptoms. Nevertheless, vitamin D, the second most reported (2 times) single micronutrient was found to cause no significant improvement in ASD core symptoms. In two cross-sectional studies (Adams et al., 2021; Hopf et al., 2016) and a randomised controlled trial (Adams et al., 2011), the use of vitamins and minerals was linked to an improvement in the core symptoms of ASD.

The eleven studies for ADHD, reported on three single micronutrients (Vitamin D, Zn and Fe) and combined minerals and vitamins. Four studies and a database analysis found that combining micronutrients was linked to significant improvement of ADHD symptoms (Calarge et al., 2010; Gordon et al., 2015; Hemamy et al., 2021; Rucklidge et al., 2010; Stevens et al., 2019). Only one trial (Johnstone et al., 2022) did not find such association. In one study, it was found that taking ADHD medicine with Fe made it work better for controlling symptoms. (Pongpitakdamrong et al., 2022). In two trials, (Mohammadzadeh Honarvar et al., 2022; Samadi et al., 2022), vitamin D supplementation did not affect the oxidative stress marker, 8-isoprostan or the inflammatory citokines, IL-6 and TNF-α. Yet in two studies, vitamin D in combination with neurofeedback therapy (Rahmani et al., 2022) and vitamin D in combination with magnesium (Hemamy et al., 2021) caused a significant reduction in ADHD scores. Zinc did not have any effect on ADHD symptoms according to the only study on zinc.

Two of the studies in Intellectual Disability (ID) used vitamin B9. One study, which used folinic acid, found that neurological functions got better (Al-Baradie & Chaudhary, 2014) while the other, which used folic acid found that developmental testing scores did not change (Han et al., 2019). For the remaining two studies, one found combined minerals and vitamins to cause significant improvement in IQ (Harrell et al., 1981), and the other, using choline, reported significant treatment effect on Elicited Imitation items recalled (Wozniak et al., 2015) .

Furthermore, in the two studies (1 case series and 1 placebo - controlled double-blind study) on Specific Learning Disorders (SLDs), vitamins B and C did not cause any significant improvement in intellectual performance over time (Kershner et al., 1977; Rankin et al., 2007).

Multivitamin users under Neurodevelopmental Motor Disorders (NMDs) reported no notable improvements in symptoms but magnesium users reported improved vocal tics (Smith & Ludlow, 2021). Nevertheless, sample size was small, and diagnosis and change in symptoms was based on self-reports, which is subjective. Also, vitamin B6 was reported by a different study to be significantly more effective than psychoeducation in reducing tics when combined with L-Theanine (Rizzo et al., 2022).

Micronutrients levels and the prevention of NDs:

In relation to ASD, Serum levels of 56 separate micronutrients were reported by 23 different studies, seven case reports and one retrospective case series. In addition, reports on 29 micronutrients from hair, saliva, urine and stool were identified from six studies. Mostly, micronutrient levels were reported as being low among this group and in many instances, the lower levels were statistically significant. Vitamins D and B, and Fe were the most studied micronutrients. In eight out of ten, serum vitamin D level was found to be significantly lower among children with ASD and correlated with ASD scores on four separate occasions (Mostafa & Al-Ayadhi, 2012; Petruzzelli et al., 2020; Qi et al., 2022; Wu et al., 2018). Maternal serum levels and intake of micronutrients (predominantly vitamin B9, prenatal vitamins/multivitamins and vitamin D) were primarily reported to be associated with lower risk of ASD in offspring . Yet, one study found no association between prenatal vitamin B9 use and risk of ASD in 3-year- old offspring (Nishigori et al., 2022).

Vitamin B9 stands out as the single vitamin that was associated with lower odds/risk of ASD even in the presence of environmental pollutants. Dosages ≥ 800 μg seem to be more advantageous in preventing ASD (Goodrich et al., 2018; Schmidt et al., 2017; Schmidt et al., 2012). However, higher levels of maternal serum folate (≥60.3 nmol/L) and B12 (≥536.8 pmol/L) at birth was reported by one study to be associated with higher odds of ASD in offspring (Raghavan et al., 2018). Another study found a weak association between higher total folate levels in early pregnancy and a higher risk of ASD in the child (Egorova et al., 2020). Prenatal vitamins/multivitamins with or without folic acid, were reported to be associated with lower odds of ASD. This association seems stronger when prenatal vitamins are started three months before pregnancy and latest by the first month of pregnancy (Schmidt et al., 2011; Schmidt, Iosif, et al., 2019).

Serum/cord levels of 40 separate micronutrients were analyzed and reported for ADHD. Fe, vitamin B, and Zn were the most reported micronutrients in descending order. Fe serum levels (mostly measured with ferritin levels) were reported as being lower in four studies (Abd El Naby & Naguib, 2018; Calarge et al., 2016; Mahmoud et al., 2011; Soto-Insuga et al., 2013) with three out of the four showing an association between Fe level and severity of ADHD. However, one study (Gottfried et al., 2013) found no difference in Fe levels between ADHD and non ADHD controls. All four studies reporting on brain iron content, suggested lower levels (Adisetiyo et al., 2019; Adisetiyo et al., 2014; Chen et al., 2022; Tang et al., 2022).Vitamin B, Zn, and I had modest repeated associations (two times each) with ADHD risk and/or symptoms.

Five studies reported on five different micronutrients (Mn, Zn, Fe, Vitamins A and D) in Intellectual Disorders (IDs). All the studies reported low serum/hair levels of micronutrients. Except for one retrospective study that used a moderate sample size, the rest utilized very small sample sizes.

Selenium was reported twice in the five studies included in the SLD group and in both cases it was found to be associated with a learning disorder (Liu et al., 2022; Xue et al., 2020). Interestingly, Xue et al. further reported that children with higher levels of urine argentum and lower level of urine selenium had a significantly higher risk of dyslexia than those with low levels of both argentum and selenium. However, this study did not consider potential confounders like renal function and BMI of the children. Another study found no correlation between offspring SLD and maternal vitamin D level in early pregnancy (Arrhenius et al., 2021).

Among the four studies on NMD, three reported on vitamin D and all reports found serum vitamin D to be significantly associated with presence or absence of tic disorder(Bond et al., 2022; Li et al., 2018; Li et al., 2017). The other reported that serum Cu, Mg, and Mn were not different for children with NMD. However, it reported lower Zn and Fe levels among NMD than typically developing children (Liu et al., 2013).

Altogether, six studies focused on a mixture of NDs. In three studies, Fe was reported to be lower in children with NDs and on an occasion, associated with disruptive behaviour (Calarge et al., 2016; De Giacomo et al., 2022; Garipardic et al., 2017). Also, maternal prenatal Se level was associated with risk of ASD and ADHD (A. S. E. Lee et al., 2021) and urinary Iodine/creatinine ratio was not associated with ASD or ADHD (Levie et al., 2020). Then, according to one study, lower levels of vitamin D in newborns are not associated with ASD or ID (Windham et al., 2019).

These findings indicate that information on micronutrients intake and levels is essential in managing the core symptoms of various NDs. Also, maternal micronutrient intakes could be a leveraging point to help reduce the risk of ASD. Therefore, policies to improve micronutrient intake in children with NDs and in women of reproductive age could be formulated or strengthened to help improve the management of NDs and reduce their occurrence.

This study has identified the need for more research in the nutritional risk factors for ADHD, ID, NMD, SLD and CD. Future research will help to better understand the nutritional management and/ or of prevention these conditions.

A noteworthy limitation is the fact that studies included in this work were of different study designs, and may thus affect the generalisation of the findings. Nonetheless, there were many controlled studies included in this study that will likely enhance the observation of real effects. Also, the methodological diversity including differences in diagnosis and outcome measurements and statistical diversity in the various studies might affect interpretation of the findings. This limitation was mitigated by thoroughly reading complete studies to interpret results correctly. Furthermore, different studies used different biological samples - blood, hair, urine, brain, and nails, to assess levels of micronutrients, which could affect the interpretation of data obtained. However, this limitation was overcome by including the sample type in the analysis.

Conclusion

Overall, there were more studies on micronutrients in relation to ASD and ADHD compared to ID, SLD, and NMD, with most of the studies coming from Europe. In the management of ASD, vitamin B was the most reported micronutrient and it was found to cause significant improvement in ASD core symptoms. Serum levels of micronutrients especially for vitamin D were significantly lower in ASD and often correlated with ASD scores. Sufficient maternal serum levels and intake of vitamin B9, prenatal vitamins/multivitamins, and vitamin D are associated with lower risk of ASD in offspring. Furthermore, combined micronutrients are more effective in managing ADHD symptoms and Fe levels are lower among children with ADHD. However, the evidence was insufficient to conclude on the potential of micronutrients in reducing the risk of ADHD, ID, SLD or NMD.

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