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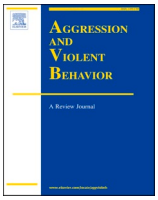

Nutritional supplementation in the management of childhood/youth aggression: A systematic review

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ABSTRACT

Excessive aggression in children and youth can lead to impairments in family, social or academic functioning. The aim of the present study was to review the evidence on the effectiveness of nutritional supplements in reducing excessive hetero-aggression in children and youth (up to 18 years). The Cochrane Library, EMBASE, MEDLINE, ProQuest Dissertations & Theses, PsycINFO, and PubMed data bases were searched for relevant studies. Altogether, 22 studies met inclusion criteria; 13 investigated the effect of macronutrients (fatty acids and amino acids), 6 studies investigated the effect of micronutrients (vitamins and minerals), while 3 studies investigated a combination of macro- and micronutrients. Out of the 22 studies, 7 reported a beneficial effect of nutritional supplementation (vitamins and minerals, essential fatty acids, or a certain combination of these); eight studies did not report a significant beneficial effect of nutritional supplementation (essential fatty acids, vitamin D, and L-tryptophan); while 7 studies reported mixed effects (vitamin B6, essential fatty acids alone and in combination with vitamins and minerals, and carnitine). The results overall suggest that there may be a role for broad-range vitamin and mineral supplements in the treatment of hetero-aggression in youth and children, while the evidence for single-nutrient supplements is quite ambiguous.

1. Introduction

Aggressive behaviors are common in children and youth and may, in some cases, be developmentally appropriate. However, pathological level of aggressive behavior in children and youth may result in impairments in family, social or academic functioning, may have acute safety risks and lead to long-term negative consequences both in the internalizing (e.g., depression) and externalizing problem domains (e.g., delinquent behavior resulting in incarceration) (Adesanya et al., 2021; Cleverley et al., 2012). When hetero-aggressive behavior becomes severe and persistent, it can also be the manifestation of a psychiatric disorder, such as oppositional defiant disorder (ODD), conduct disorder (CD), attention deficit hyperactivity disorder (ADHD), autism spectrum disorder (ASD), trauma-related disorders and others (Ford et al., 2012).

The neurobiology of excessive or pathological aggression is complex and poorly understood. Neurochemical systems can impact aggression in at least two ways: by influencing central nervous system development during critical periods and modulating neuronal functioning of the already developed nervous system (Rosell & Siever, 2015). Both the serotonin and dopamine systems have been shown to play a role in modulating aggression in addition to GABA, oxytocin, testosterone and cortisol (Siever, 2008). Several important gene by environment interactions also exist (Siever, 2008), including specific genetic polymorphisms and early adversity that in combination may predispose to aggression (Rosell & Siever, 2015).

First-line treatment recommendations for the treatment of maladaptive/excessive aggression in children and youth include psychosocial interventions according to clinical practice guidelines (T-MAY guidelines) (Rosato et al., 2012). The use of psychiatric medications may be considered once psychosocial interventions have been shown to be inadequate or unfeasible; treatment guidelines support medications from a variety of classes to treat excessive aggression in youth (Gorman

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et al., 2015). In summary, psychostimulants (medications that increase the activity of the central nervous system) have been shown to be highly effective in decreasing aggressive behavior in children and youth with ADHD with a minor side effect profile, whereas risperidone has shown moderate efficacy for reducing aggressive behavior in children and youth with normal and low IQ, though the side effect burden is high (Rosato et al., 2012). Low quality evidence provides some support for the use of haloperidol, valproate, lithium and carbamazepine to reduce aggression in children with conduct disorder, though side effect burden is significant and these options are largely not recommended by some more recent guidelines (Gorman et al., 2015). As such, several limitations exist among available pharmacological treatment options related to access, safety, efficacy, as well as patient and family preferences (Barzman & Findling, 2008; Magalotti et al., 2019; Pisano & Masi, 2020).

Adaptive aggression regulation is dependent on both the healthy development of the nervous system in childhood and adolescence as well as an ongoing balance between bottom-up subcortical processes and top-down cortical modulation (Siever, 2008). All of these processes are reliant on – among other factors – the adequate level of nutrients available in the body to support the growth and optimal functioning of the nervous system. For instance, omega-3 fatty acids are necessary for general neurodevelopment as they are building blocs of brain cell membranes including neuronal synapses (Gajos & Beaver, 2016). On the other hand, micronutrients (vitamins and minerals) serve as co-factors in the synthesis of neurotransmitters (e.g., serotonin, dopamine, GABA) (Rucklidge et al., 2021). Consequently, adaptive aggression regulation is also dependent on nutritional status, which if suboptimal, can be improved by nutritional supplementation. Nutritional supplements are widely acceptable and commonly used. According to a Canadian general population survey, 46.9 % of women and 33.5 % of men reported taking at least one nutritional supplement in the month preceding the survey (Vatanparast et al., 2010). The same values in a study conducted in the United States were 53 % and 44 %, respectively (Bailey et al., 2010), while yet another study reported that 33 % of children and adolescents used dietary supplements in 2013–2014 (Qato et al., 2018).

The potential of nutrients such as vitamins, minerals and amino acids to reduce aggression and violence is an active area of study within the field of nutritional psychiatry (Rucklidge et al., 2015). Moreover, a higher intake of processed foods, red meat, high-fat dairy products and high-sugar foods at age 11 years was prospectively associated with increased externalizing behaviors at age 14 in a large prospective study of Australian youth (Trapp et al., 2016) indicating that the over-consumption of certain nutrients or substances could also lead to increase in the occurrence of maladaptive behaviors. While dietary manipulations should be the first choice when trying to improve the nutritional status of individuals, such attempts often fail due to a variety of reasons. It is well-documented, for example, that difficulties with adherence to dietary modifications hinders the effectiveness of such interventions (World Health Organization, 2003). Further, above-average nutritional needs due to inherited metabolic characteristics, chronic stress, use of certain medications, or poor gut health as well as reduced nutrient content of natural food sources are all potential factors that can prevent dietary modifications reaching their intended purpose (Rucklidge et al., 2021).

Extant reviews aiming to synthesize the growing amount of evidence on the role of nutrition in the management of aggression have focused either on a single or a single group of nutrients (Gajos & Beaver, 2016; Hibbeln & Gow, 2014), more complex outcomes and not aggression per se (Rucklidge & Kaplan, 2013), or adults (Qureshi et al., 2021). Therefore, the aim of the current study was to synthesize the evidence accumulated to date on nutritional supplement interventions for the management of hetero-aggressive behavior in children and youth in order to provide 1) clinicians with a better understanding of this group of potential treatment options, and 2) researchers with a synthesis of the current evidence base and potential directions for future research.

2. Methods

2.1. Search strategy

The protocol of the present systematic review was registered in the International Prospective Register of Systematic Reviews (PROSPERO) on October 4th, 2018 under record # 106663. The following six electronic databases were searched: Cochrane Library, EMBASE, MEDLINE, ProQuest Dissertations & Theses, PsycINFO, and PubMed. Searches were initially conducted on July 15, 2018, and a follow-up search was completed on March 30, 2020. The search strategy included a list of terms related to nutritional supplementation, which were combined with terms relating to aggression using the Boolean operator "AND" (see full list of search terms in Table 1). Terms were searched in the study title and abstract. Associated subject headings were also utilized to create a more comprehensive search strategy. The electronic data base searches were conducted by FMQ after consulting with an expert librarian.

2.2. Inclusion and exclusion criteria

Articles were included in the qualitative evidence synthesis if they investigated the effectiveness of nutritional supplementation in reducing violent or hetero-aggressive behavior in individuals younger than 18 years of age [the literature on individuals 18 years or older has been summarized in the work of Qureshi and colleagues (Qureshi et al., 2021)]. The term 'nutritional supplement' was defined as a manufactured product (in the form of pills, capsules, tablets, or liquids) intended to supplement diet with substances that have been confirmed as being essential to life (Meyers et al., 2006). Such formulas include micronutrients such as vitamins (e.g., vitamin A, vitamin B etc.) and minerals (e.g., Ca, Mg, Zn etc.) or macronutrients (e.g., fatty or amino acids etc.) or a combination of these. Supplementation was defined as the consumption of nutritional supplements in addition to diet; that is, studies focusing on diet in itself or changes in diet were considered to be outside of the scope of the current review to permit a feasible focus.

Violent / aggressive behavior was defined as intentionally causing or attempting to cause harm or damage to something or somebody other than the acting person; that is, our primary focus was hetero- and not auto-aggression. It included both reactive aggression, that is, impulsive violence or threat-driven aggression, as well as proactive aggression or violence committed with a purpose to increase one's dominance or to obtain property (Fossati et al., 2009). This study focused on *behavioral*-level violence and aggression in real-life (non-simulated) settings. We decided to focus on behavioral aggression as it has more severe consequences both for the aggressor, the victim, and the social environment than aggressive *thoughts* or hostile *emotions*. In addition, it seems plausible to assume that the regulation of aggressive *behavior* may involve somewhat different neurobiological correlates than the *experience* of anger [cf. (Denson et al., 2009; Lotze et al., 2007)]; and, therefore, the relationship of these neurobiological processes with nutritional status might differ.

In accordance with these considerations, studies were excluded if they investigated the following: 1) aggressive / angry / hostile *emotions* or *thoughts* without observable behaviors; 2) aggressive tendencies presented in simulated environments (e.g., level of aggression expressed in a video game play situation, which is thought to be qualitatively different from real-life situations); 3) self-harm only (however, hetero-aggressive aspects of studies with a combined focus on aggression targeting the self and others were considered); and 4) complex outcome variables in which aggression was just marginally represented [Conduct Subscale of the Strengths and Difficulties Questionnaire (Goodman, 2001) or Irritability Subscale of the Aberrant Behavior Checklist (Aman et al., 1985)]. In terms of study design, the current review considered controlled trials (randomized or not), observational cohort studies, and case series. Only prospective studies with a minimum of two assessment

Table 1
Author-identified key words and database-specific subject headings used in the searches.

	Ovid (EMBASE, MEDLINE, PsycINFO)	Cochrane Library	PubMed
Author-identified keywords related to aggression	Aggression, Violent, Violence		
Data-base specific subject headings related to aggression	Violence / assault / battering, Physical abuse, Aggression / aggressiveness	Aggression, Violence, Physical Abuse	Aggression, Violence, Physical Abuse
Author-identified keywords related to nutritional supplementation	Mineral*, Vitamin*, Micronutrient*, Nutraceutical*, Nutrient supplement*, Dietary supplement*, Nutritional supplement*, Nutrition, Nutrient*, Supplement*, Fatty acid, Amino acid*		
Data-base specific subject headings related to nutritional supplementation	Trace element, Mineral, Vitamin/multivitamin/provitamin, Diet supplementation, Dietary supplement, Nutrition supplement / minerals plus multivitamins, Nutrition, Nutrient / inorganic nutrient / macronutrient / nutrient solution / organic nutrient / phytonutrient / plant nutrient, Fatty acid, Amino acid	Minerals, Vitamins, Micronutrients, Nutrition therapy, Trace elements, Micronutrients, Dietary supplements, Fatty Acids, Amino acids	Vitamins, Trace elements, Minerals, Dietary supplements, Fatty acids, Amino acids

points for aggression were considered. No restrictions were placed regarding year of publication; however, only English language studies were considered.

2.3. Screening

The database searches retrieved a total of 11,955 results, which were uploaded onto the *EndNote* software (version: *EndNote* X8) to organize and compile studies. After removing duplicates, a remainder of 8381 records were exported into the *Rayyan QCRI* web application, which was designed to help systematic review authors to complete primary screening of studies in a time-efficient and organized way employing natural language processing, artificial intelligence, and machine learning technologies. Primary screening resulted in 61 potentially relevant records. Additional records were identified by hand-searching the reference lists of eligible studies and reviews on the topic. The primary screening was completed by FMQ, while checking for eligibility criteria were completed by RQ and BKT independently and any inconsistencies were resolved by consensus.

2.4. Data extraction

Data extraction was completed by two independent scorers (RQ and MW). Any discrepancies were resolved via discussion involving the senior author (BKT) of the project. Methodological quality of the studies was assessed using the 2018 version of the Mixed Methods Appraisal Tool (MMAT) (Hong et al., 2018), which is especially useful in the case of systematic reviews summarizing the results of studies with a mixture of study designs (the design-specific items can be found in the manual of the tool, which is located in the public domain and can be accessed at: http://mixedmethodsappraisaltoolpublic.pbworks.com/w/file/fetch/127425851/MMAT_2018_criteria-manual_2018-04-04.pdf). An ad hoc supplementary question was also added to the MMAT to evaluate the quality of statistics as this aspect is not adequately covered in the MMAT. Quality of statistics was considered appropriate if study authors 1) used adequate statistical tests considering the research question and type of data, 2) reported the results of the statistical tests including probability values, and 3) reported effect size indicators as well. An ad hoc summary score (ranging from 0 to 8) was also created to facilitate the comparison of studies in terms of overall methodological quality regardless of their designs.

Beyond methodological quality, the following data were extracted from each study: number of participants in the intervention and control group, sex of participants, age, diagnosis/condition (if any) of participants, supplementation given, placebo content used (if any), parallel psychiatric treatment (pharmacotherapy and/or psychotherapy), data on default diet or serum nutrient level, assessment timeline (e.g., length of supplementation and follow-up), violence/aggression indicator, primary (related to violence/aggression) as well as secondary results (e.g., outcome data on psychopathology), and side effects in relation to the nutritional supplements. An overall conclusion about whether beneficial treatment effects were observed in terms of excessive hetero-aggression was also formed with three options: yes, no, and mixed (if different effects were observed across multiple aggression-related outcome variables or subgroups of the sample). If any information was missing or unclear, the original study investigators were contacted for clarification.

Finally, a formal statistical analysis (one-way analysis of variance) was also conducted to examine if overall methodological quality (using the methodological summary score described above) was independent of the reported effectiveness of the intervention (using the overall study conclusion variable). The software Statistical Package for the Social Sciences, Version 27 (IBM SPSS, 2020) was used for the analysis. Eta squared was used to express effect size.

3. Results

3.1. Characteristics of included studies

Altogether, 73 records were assessed in full text and finally 22 studies met eligibility criteria (reasons for exclusion are described in more detail in Fig. 1). Of the 22 included studies, 16 were randomized controlled trials and 6 were single group, pre-post studies. Study design and detailed methodological quality assessment for each study is outlined in Table 2. Altogether, 13 studies investigated children with neurodevelopmental (including ADHD or autism) or disruptive, impulse control and conduct disorders (e.g., oppositional-defiant disorder or conduct disorder). Out of the 13 studies, 5 included participants diagnosed with ADHD; 4 studies included a heterogeneous sample of participants diagnosed with different neurodevelopmental or disruptive, impulse control or conduct disorders; 2 studies included participants with various neurodevelopmental disorders; 1 study included participants diagnosed with autism spectrum disorder; and finally 1 study included participants with a disruptive, impulse control or conduct disorder. In addition, two studies investigated children with repeated acts of juvenile delinquency, of which one focused on incarcerated youths, while the second focused on school children without formal diagnoses. Three studies investigated children with other neurological or psychiatric illnesses (epilepsy, mood, and anxiety disorders), and 4 studies investigated children with no reported illnesses.

Across the 22 studies, the total sample size was 2931, ranging from 9 to 940 participants per study. Further, 16 studies investigated a mixed sample of males and females, 4 studies investigated only male samples, while 1 study investigated a female-only sample. The remaining 1 study did not specify the sex composition of the sample. The majority of the studies also contained information on the diet / pre-intervention serum nutrient level (19 out of 22 studies) and parallel psychiatric treatment or the lack thereof (17 out of 22 studies) of participants. Detailed description of these data can be found in Supplementary Table 1.

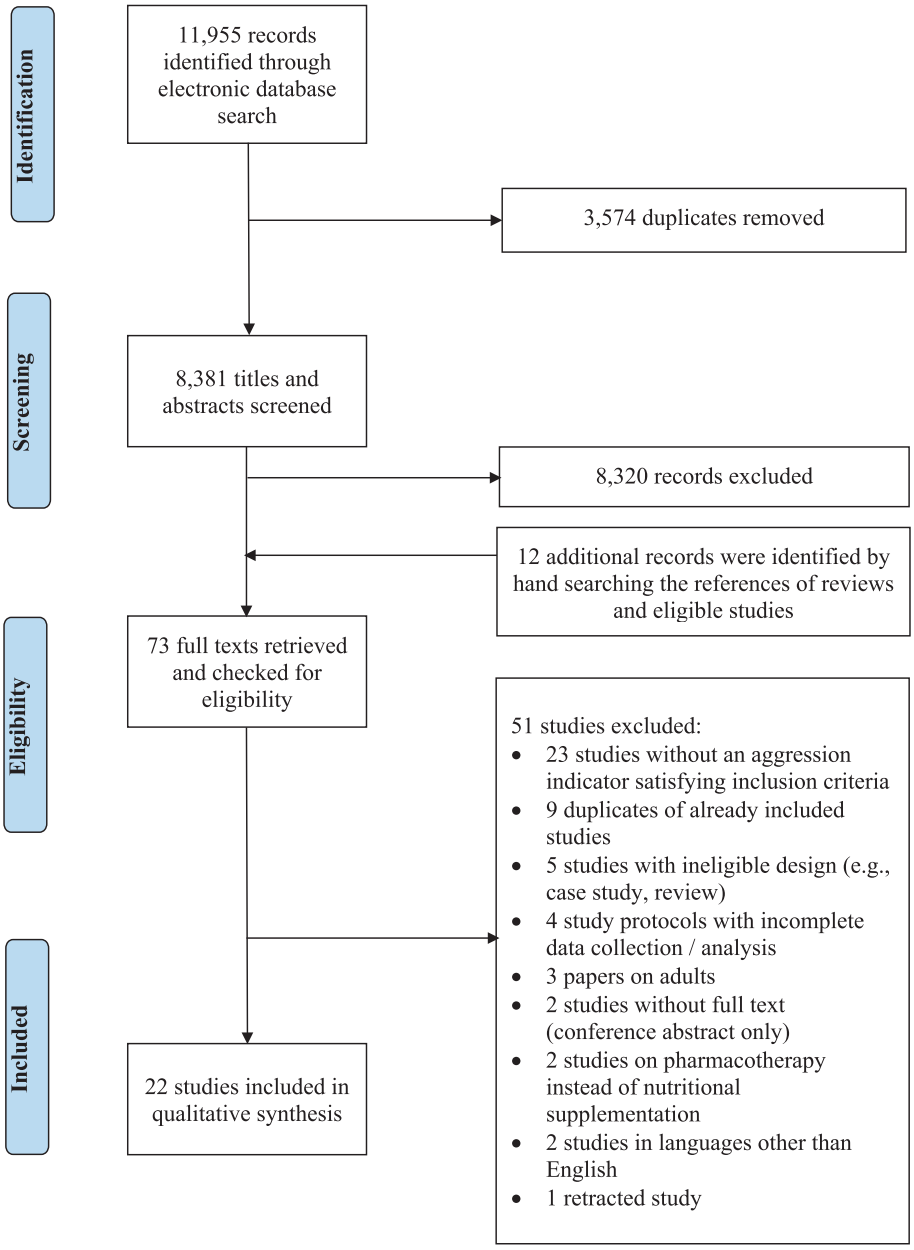

Fig. 1. Systematic review flow diagram.

3.2. Data on supplement content and assessment of outcome variables

Out of the 22 included studies, 13 investigated the effect of macronutrients (fatty acids and amino acids), 6 studies investigated the effect of micronutrients (vitamins and minerals), while 3 studies investigated a combination of macro and micronutrients. Six studies examined single nutrients, whereas 16 studies investigated multi-nutrient supplementation. The length of supplementation was 14.8 weeks on average (SD = 6.8 weeks, Median = 13 weeks). Information on placebo content can be found in Supplementary Table 2.

Most studies used a single aggression indicator (17 studies) but authors of a few studies used multiple assessment tools (4 studies), while the authors of one study created aggregate indexes out of multiple assessment tools using factor analytic techniques. Most frequently used violence and aggression outcome indicators included the Aggression Subscale of the Child Behavior Checklist [(Achenbach & Ruffle, 2000), 8 studies], the Buss-Perry Aggression Questionnaire [(Buss & Perry, 1992), 3 studies], ad hoc questions assessing aggression (3 studies), the Reactive-Proactive Aggression Questionnaire [(Raine et al., 2006), 3 studies], and the Youth Self Report [(Ebesutani et al., 2011), 3 studies]. Further, the Modified Overt Aggression Scale (Knoedler, 1989) was used in 2 studies; authors of additional 2 studies used institutional (school / prison) infraction records, while another 2 studies used the teacher and parent version of the Children's Aggression Scale (Halperin et al., 2002). Other aggression and violence outcome indicators such as the Meanwood Park Hospital Behavior Rating Scale and visual analogue scales (Ghose, 1983), Conner's Parent Rating Scale (Conners, 2001), and Walsh-Isaacson Behavior Scale (Walsh et al., 1997) were used only by one study each. Altogether, 16 studies used observer-rated measurement tools to assess aggression/violence, three used self-reported tools, while additional three studies employed a combination of these two approaches. Study-level data on the self- versus observer-rated nature of aggression measurement can be found in Supplementary Table 2.

Table 2
Methodological characteristics of the studies included.

Study	Design	MMAT S1	MMAT S2	MMAT1	MMAT2	MMAT3	MMAT4	MMAT5	Statistics	Total score
Studies on patients with diagnosed neurodevelopmental or disruptive, impulse control and conduct disorders										
Aman et al. (1987)	Double-blind, randomized, placebo-controlled, crossover trial	1	1	0	0	1	1	1	0	5
Bos et al. (2015)	Double-blind, randomized, placebo-controlled trial	1	1	1	1	1	1	1	0	7
Dean et al. (2014)	Double-blind, randomized, placebo-controlled, crossover trial	1	1	1	1	1	1	1	1	8
Hambly et al. (2017)	Single group, pre-post design using cluster randomized sampling	1	1	1	1	1	0	1	1	7
Hirayama et al. (2004)	Double-blind, randomized, placebo-controlled trial	1	1	1	1	1	1	1	0	7
Johnson et al. (2010)	Open label, randomized, controlled trial	1	1	0	1	1	1	1	0	6
Mousain-Bosc et al. (2006)	Single group, pre-post design	1	1	1	1	1	0	1	0	6
Ooi et al. (2015)	Single group, pre-post design	1	1	1	1	1	1	1	1	8
Perera et al. (2012)	Double-blind, randomized, placebo-controlled trial	1	1	1	1	1	1	1	1	8
Raine et al. (2016)	Single-blind, randomized, stratified, factorial trial	1	1	1	1	0	0	1	1	6
Raine et al. (2018)	Double-blind, randomized, placebo-controlled trial	1	1	1	1	1	1	1	1	8
Van Oudheusden and Scholte (2002)	Double-blind, randomized, placebo-controlled, double-crossover trial	1	1	0	1	1	1	1	0	6
Walsh et al. (2004)	Single group, pre-post design using cluster randomized sampling	1	1	1	1	1	1	1	0	7
Studies on patients with other medical conditions (other psychiatric, neurological, or general somatic illness)										
Schoenthaler et al. (1997)	Double-blind, randomized, placebo-controlled trial	1	1	1	1	1	1	1	0	7
Schoenthaler and Bier (2000)	Double-blind, randomized, placebo-controlled trial	1	1	1	1	1	1	1	0	7
Ahmadabadi et al. (2017)	Double-blind, randomized, placebo-controlled, crossover trial	1	1	0	1	1	1	1	0	6
Ghose (1983)	Double-blind, randomized, placebo-controlled, crossover trial	1	1	0	1	1	1	1	0	6
Kaplan et al. (2004)	Single group, pre-post design	1	1	1	1	1	1	1	1	8
Studies on general adolescent population.										
Bahrami et al. (2018)	Single group, pre-post design using cluster randomized sampling	1	1	1	1	1	1	1	0	7
Hamazaki et al. (2008)	Double-blind, randomized, placebo-controlled trial	1	1	1	1	1	1	1	0	7
Itomura et al. (2005)	Double-blind, randomized, placebo-controlled trial	1	1	1	1	1	1	1	0	7
Raine et al. (2015)	Double-blind, randomized, placebo-controlled trial	1	1	1	1	1	1	1	1	8

3.3. Data on primary outcomes

Out of the 22 studies, 7 reported a statistically significant, beneficial effect of nutritional supplementation on violence and aggression indicators. The supplements in these studies were vitamins, minerals, omega-3 fatty acids, or a certain combination of these (i.e., fatty acids and amino acids in addition to minerals and vitamins). Seven studies documented mixed effects (i.e., beneficial effects along certain indicators or in certain subsamples but not in others). Supplements in these studies were vitamin B6, supplements containing fatty acids and vitamins, omega-3 fatty acids (DHA and EPA) alone, and carnitine. Finally, eight studies reported no statistically significant treatment benefit regarding excessive hetero-aggression. Supplements in these studies were fish oil supplementation with only eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), omega-3 fatty acids and essential fatty acids, vitamin D, and L-tryptophan. Detailed information on the results in each study, including the supplements and their dosages, are described in Table 3.

The difference in methodological quality between studies with positive ($n = 7$, $M_{\text{methodology total score}} = 7.14$, $SD = 0.69$), null ($n = 8$, $M_{\text{methodology total score}} = 6.75$, $SD = 1.04$) or mixed ($n = 7$, $M_{\text{methodology total score}} = 6.86$, $SD = 0.90$) results were not statistically significant ($F = 0.377$, $p = 0.691$) and the magnitude of the omnibus group difference was small ($\eta^2 = 0.038$).

3.4. Data on non-aggression-related outcomes

Altogether, 6 studies reported beneficial effects of nutritional supplementation with regards to non-aggression-related indicators, including reduced depression, improved health-related quality of life, improved family functioning, less hyperactivity, a decrease in autism spectrum disorder symptoms, increased social motivation, decreased social problems, lessened attention problems, and decreased non-violent rule infractions. More detailed information on the non-aggression-related results of these studies can be found in Supplementary Table 3. Only one study did not show any beneficial effects of nutritional supplementation across the non-aggression-related outcomes (hyperactivity, destructiveness, antisociability, cooperation, restlessness, energy, and seizure frequency). An additional 13 studies reported mixed effects of treatment in relation to non-aggression-related outcomes; in these studies, memory and attention, visual and motor skills, school behavior, as well as mood and disruptive behaviors showed improvement in

Table 3
Main results of the studies included.

Study	Sample	N	Supplement [duration of supplementation]	Results	Treatment benefit
Studies on patients with diagnosed neurodevelopmental or disruptive, impulse control and conduct disorders					
Aman et al. (1987)	Subjects with severe inattention, impulsivity, and overactivity from early childhood but at least for one year (87 % males, M_{age} = 8.9 years, SD_{age} = 1.9 years)	31	Essential fatty acid (Efamol): 3 capsules, consumed twice/day, containing 360 mg of linoleic acid and 45 mg of gamma-linoleic acid. [6 weeks]	No significant change between intervention and control group observed for Child Revised Behavior Problem Checklist, socialized aggression subscale (*p*-value not reported).	No
Bos et al. (2015)	Adolescent males diagnosed with attention deficit and hyperactivity disorder (M_{age} = 10.6 years, SD_{age} = 2.0 years, $Range_{age}$ = 8–14 years)	76	Omega-3 fortified margarine: 10 g/day, full fat, 80 % margarine (0.65 g EPA, 0.65 g DHA, 2.08 g MUFA, 2.66 g SAFA, 2.66 g PUFA, 0.1 g trans-FA, 0.07 g ALA, 1.0 g LA, 0.03 g AA, <1 g protein, 6.4 mg Vitamin E). [16 weeks]	No significant effects of intervention observed on Child Behavior Checklist, Aggressive Behavior Subscale scores (*p*-value not reported)	No
Dean et al. (2014)	Children diagnosed with oppositional defiant disorder or conduct disorder and ADHD, exhibiting impulsive aggressive behaviors for at least 6 months (81 % males, M_{age} = 10.3 years, SD_{age} = 2.2 years, $Range_{age}$ = 6–17 years)	21	Fish oil: 4 g capsule/day, containing 400 mg eicosapentaenoic acid and 2000 mg docosahexaenoic acid. [6 weeks]	No effect of intervention was observed, either for the parent-rated Children's Aggression Scale subscales or for the total score (p = 0.82, Cohen's d = 0.19). Also, no effect observed on the Modified Overt Aggression Scale total score (p = 0.79, Cohen's d = 0.09).	No
Hambly et al. (2017)	Adolescent males diagnosed with neurodevelopmental disorder/no formal diagnosis, exhibiting violent and aggressive behaviors for at least 6 months (M_{age} = 8.4 years, SD_{age} = 2.9 years, $Range_{age}$ = 4–14 years)	31	Capsules with micronutrient; dose calculated based on weight, e.g., a 25 kg subject received 460 mg of vitamin C, 23 mg of vitamin B6, and 57.5 mg of P5P in the morning; and 460 mg of vitamin C, 34.5 mg of zinc, 368 (international units) IU of vitamin E, 920 (micrograms) mcg of biotin, 46 μg of chromium, and 11.5 μg of selenium in the evening. [16 weeks]	Subjects showed a significant decrease in aggression and violent behaviors in 8 weeks, for Modified Overt Aggression Scale (MOAS) ($p < 0.001$) and parent-rated Children's Aggression Scale (CAS-P; $p < 0.001$ to $p = 0.002$) scores. Significant ($p < 0.001$) improvement with large effect size (Cohen's d = 1.26) for the MOAS from baseline to week 16. A significant improvement in parent-reported total aggression for all CAS-P subscales ($p < 0.001$ to $p = 0.02$) from baseline to week 16. Medium to large effect size for all subscales of the CAS-P (Cohen's d = 0.72–1.43) except the use of weapons subscale (Cohen's d = 0.42) between baseline and week 16.	Yes
Hirayama et al. (2004)	Subjects diagnosed with attention deficit / hyperactivity disorder and often comorbid with other psychiatric disorders (80 % males, $Range_{age}$ = 6–12 years, $Median_{age}$ = 9 years)	40	Supplements taken through food consumption: fermented soybean milk (600 mg DHA/125 ml, 3/week), bread rolls (300 mg DHA/45 g, 2/week) and steamed bread (600 mg DHA/60 g, 2/week) for 2 months. Average intake of omega-3 fatty acids from these foods was 3600 mg docosahexaenoic acid (DHA) and 700 mg eicosapentaenoic acid (EPA)/week. [8.5 weeks]	Changes in aggression scores (based on parent and teacher rated scores on ad-hoc questions) did not significantly change between the control and intervention groups (*p*-value not reported). Significant intragroup difference was observed in the intervention group (p = 0.053).	Mixed
Johnson et al. (2010)	Young children diagnosed with autism spectrum disorder, and other neurodevelopmental disorders (sex not specified, $M_{age\ of\ intervention\ group}$ = 44.7 months, $SD_{age\ of\ intervention\ group}$ = 7.6 months, $M_{age\ of\ control\ group}$ = 38.7 months, $SD_{age\ of\ control\ group}$ = 8.5 months)	23	Docosahexaenoic acid (DHA): 2 capsules/day, daily dose of 400 mg (28 mg/kg dose). An average 30-month-old child is 13.5 kg, and an average 54-month-old child is 16 kg. Therefore, a 28 mg/kg dose is ~400 mg daily. [13 weeks]	No significant difference observed between intervention and control group in scores for Child Behavior Checklist, Aggression Subscale, from baseline to 3 months (p = 0.532).	No
Mousain-Bosc et al. (2006)	Subjects diagnosed with attention deficit hyperactivity disorder (68 % males, M_{age} = 6.5 years)	40	Mg-Vitamin B6 regimen: 6 mg/kg/d magnesium and 0.6 mg/kg/d vitamin B6. [9 weeks]	Hyperemotivity/aggressiveness (based on ad hoc question) was significantly reduced in subjects ($p < 0.0001$).	Yes
Ooi et al. (2015)	Subjects diagnosed with autism spectrum disorder (88 % males, M_{age} = 11.7 years, SD_{age} = 3.1 years, $Range_{age}$ = 7–18 years)	41	Essential fatty acid (Efamol Efalex): 15 ml, twice daily; 1 g per day of omega-3 fatty acids, containing 840 mg DHA, 192 mg EPA, 1278 mg pure evening primrose oil (66 mg arachidonic acid and 144 mg gamma-linolenic acid, 60 mg vitamin E, and 3 mg thyme oil). [12 weeks]	No significant decrease in Child Behavior Checklist, Aggressive Behaviors Subscale scores from pretreatment to posttreatment at 12 weeks (authors erroneously reported a *p*-value of 4.96 in the paper, we infer that it is 0.496; Cohen's d = 0.09)	No
Perera et al. (2012)	Subjects diagnosed with attention deficit hyperactivity disorder (73.4 % males, $M_{age\ of\ intervention\ group}$ = 9.4 years, $SD_{age\ of\ intervention\ group}$ = 1.5 years, $M_{age\ of\ control\ group}$ = 9.2 years, $SD_{age\ of\ control\ group}$ = 1.5 years, $Range_{age}$ = 6–12 years)	94	Omega-3 and − 6 fatty acids (Vegepa): 2 capsules per day in 2 doses. Contains fish oil and cold-pressed evening primrose oil in the ratio 1.6:1, 296.37 mg omega-3, 180.75 mg omega-6. [26 weeks]	Subjects in the intervention group showed significantly larger improvements in aggressiveness (from parent-administered ad hoc ADHD symptom improvement checklist) at both at 3 ($p < 0.001$, Cohen's d = 0.99) and 6 ($p < 0.001$, Cohen's d = 1.42) months.	Yes
Raine et al. (2016)	Subjects diagnosed with full or borderline conduct disorder or oppositional defiant	290	Omega-3 fatty acids: 200 ml daily drink, containing 1000 mg of omega-3 (300 mg of DHA, 200 mg of EPA, 400 mg of alpha-	The intervention group scored significantly lower than controls for child-reported externalizing behavior	Mixed

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Table 3 (*continued*)

Study	Sample	N	Supplement [duration of supplementation]	Results	Treatment benefit
	disorder (53 % males, $Range_{age}$ = 11–12 years)		linolenic acid, and 100 mg of DPA); 12 vitamins +7 minerals (for detailed content of product, see study description in Supplementary Table 2). [13 weeks]	factor score at 3 months ($p = 0.044$, Cohen's d = 0.33); at 6 months, the combined CBT + intervention group scored lower than the CBT only group (p = 0 0.031, Cohen's d = 0.35). The intervention only group scored lower than controls for the child-reported aggressive-reactive factor score at 3 months ($p = 0.006$, Cohen's d = 0.45); at 6 months, the combined intervention + CBT group showed significantly lower scores compared to the CBT only group ($p = 0.03$, Cohen's d = 0.35) with lower scores compared to controls ($p = 0.055$). There were no differences across groups for child-reported callous-proactive aggression factor scores or for parent-reported externalizing behavior factor scores.	
Raine et al. (2018)	Subjects diagnosed with oppositional defiant disorder, conduct disorder, or attention deficit hyperactivity disorder (87 % males, $Range_{age}$ = 7–16 years)	282	Omega-3 (ω-3) supplementation: 4 capsules/day, 500 mg. Contains 5.6 mg vitamin E, 102.8 mg of DHA, 26.6 mg of DPA, and 151 mg of EPA). Total daily dosage of 1.12 g of ω-3 (411.2 mg DHA, 106.4 mg DPA, and 604 mg of EPA). [26 weeks]	A significant group × time interaction was observed on Reactive-Proactive Aggression Questionnaire, Reactive Aggression Subscale scores ($p = 0.002$). Univariate tests were significant for the intervention-only group ($p = 0.005$), the intervention + social skills group ($p = 0.001$), and the controls ($p = 0.031$). For the intervention-only group, reactive aggression was significantly reduced compared to baseline values at 3 months ($p = 0.018$, Cohen's d = 0.19) and 6 months ($p = 0.042$, Cohen's d = 0.21). There was a significant long-term decline in reactive aggression from 0 to 12 months ($p = 0.028$, Cohen's d = 0.29); no further baseline–post-treatment effects had significant changes ($p > 0.13$). For the intervention + social skills group, there was a significant long-term drop in reactive aggression at 12 months compared to baseline ($p = 0.041$, Cohen's d = 0.24); no further baseline–post-treatment comparisons had significant changes ($p > 0.11$). In the control group, no baseline–post-treatment comparisons showed significant changes for reactive aggression ($p > 0.13$). The group × time interaction was non-significant for proactive aggression ($p = 0.36$).	Mixed
Van Oudheusden and Scholte (2002)	Adolescent males diagnosed with attention deficit hyperactivity disorder ($Range_{age}$ = 6–13 years)	21	Carnitine: 100 mg/kg 2 times/day after meals, with a maximum of 4 g. [24 weeks]	Responders receiving carnitine treatment showed a significant improvement on the parent-rated Child Behavior Checklist, Aggressive Behavior Subscale scores, compared to baseline ($p < 0.0001$). Non-responders receiving carnitine treatment showed no improvement in aggressive behavior scores, compared to baseline ($p = 0.3$).	Mixed
Walsh et al. (2004)	Young outpatients with a diagnosis of ADD, conduct disorder, oppositional-defiant disorder, or other behavioral disorders (72 % males, $Range_{age}$ = 3–55 years, $Median_{age}$ = 11.5 years)	207	Regimen of specific amino acids, vitamins, and minerals developed for each subject based on diagnosed imbalances. Options given of taking capsules, tablets, powders, or liquids (average involved 5–10 capsules, taken twice daily). Regimen content included zinc, cysteine, manganese, pyridoxine, ascorbic acid, Vitamin E, folic acid, cobalamin, niacinamide, methionine, calcium, magnesium, Vitamin D, pyridoxal-5-phosphate, Vitamin C, selenium, metallothionein, and chromium. [17.4–34.8 weeks]	Compliance rate was 76 % according to family members. In treatment-compliant assaultive patients, 92 % exhibited reduced frequency of assault, and 58 % achieved elimination of behavior. In treatment-compliant destructive behavior patients, 88 % exhibited reduced frequency of destructive episodes, and 53 % achieved elimination of behavior. Treatment-compliant subjects showed lower assaultive and destructive frequencies of behavior after intervention ($p < 0.001$). Statistically significant reduction seen in frequency of assaults ($t = 7.94$; $p < 0.001$) and destructive incidents ($t = 8.77$; $p < 0.001$).	Yes

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Table 3 (*continued*)

Study	Sample	N	Supplement [duration of supplementation]	Results	Treatment benefit
Studies on patients with other medical conditions (other psychiatric, neurological, or general somatic illness)					
Schoenthaler et al. (1997)	Incarcerated juveniles exhibiting multiple psychological problems and repeat delinquency; diagnosis of aggressive behavior (66 % males, M_{age} = 15.2 years, $Range_{age}$ = 13–17 years)	62	Supplements with 12 vitamins +11 minerals: contains 100 % of the US recommended daily allowance (RDA) for minerals and 300 % of the US RDA for most vitamins, however Vitamin A and folate were set at the US RDA. For detailed content of product, see study description in Supplementary Table 2. [13 weeks]	Based on prison infraction records, no significant difference observed at baseline, between study groups (p = 0.97). The main effect of grouping was significant (p = 0.04). Among 10 subjects who maintained their normal or low blood concentrations of vitamins throughout the trial, there was no significant change in violence. Among the 16 subjects who corrected their low blood vitamin concentrations during intervention there was a drop in violent acts from 131 during baseline to 11 during intervention.	Yes
Schoenthaler and Bier (2000)	School children formally disciplined for violating rules and tested for juvenile delinquency (69 % males, $Range_{age}$ = 6–12 years)	80	Vitamins tablets: Nutrients were set at approximately 50 % of the U.S. RDA for all vitamins and most minerals but were lower for bulky nutrients like calcium and magnesium. For detailed content of product, see study description in Supplementary Table 2. [17.4 weeks]	Based on school infraction records, children in the intervention group were disciplined 47 % less during the intervention period than the control group. The difference between the groups in rule violations during the intervention period was statistically significant (p = 0.038) even after controlling for the baseline value.	Yes
Ahmadabadi et al. (2017)	Young, adolescent patients diagnosed with seizure disorders/ epilepsy (48 % males, $M_{age\ of\ intervention\ group}$ = 39.2 months, $SD_{age\ of\ intervention\ group}$ = 11.6 months, $M_{age\ of\ control\ group}$ = 37.4 months, $SD_{age\ of\ control\ group}$ = 10.4 months, $Range_{age}$ = 2–15 years)	77	Vitamin B6 in combination with phenobarbital (40 mg tablets): contains 100–150 mg vitamin B6. [13 weeks]	No significant difference between the intervention and control group before cross-over (p = 0.15) or after cross-over (p = 0.60) on Conner's Parent Rating Scale, Aggression Subscale scores. Aggression values in both groups were lower at the end of the supplementation phase compared to the end of the placebo phase, however, this within-group difference was significant (p = 0.01) only in one of the two study groups (in the other group: p = 0.88).	Mixed
Ghose, 1983	Adolescent males diagnosed with epilepsy/ hyperkinesia/hyperactive child syndrome (M_{age} = 11.3 years, $Range_{age}$ = 7–14 years)	11	L-Tryptophan: Given orally 3 times/day at 40 mg/kg body weight. Total daily dose varied between 1200 and 2000 mg) [5 weeks]	No significant difference between the intervention and control group on the Meanwood Park Hospital Behavior Scale, Aggressiveness Subscale, or the aggressiveness visual analogue scale (p-value and effect size not reported).	No
Kaplan et al. (2004)	Subjects diagnosed with anxiety or mood disorders (64 % males, M_{age} = 11.4 years, SD_{age} = 2.6 years, $Range_{age}$ = 8–15 years)	9	E.M. Power + supplementation: 18 capsules/day; powder can be mixed in juice. Contains 36 minerals, amino acids, antioxidants, and vitamins (for detailed content of product, see study description in Supplementary Table 2). [8–17 weeks]	Subjects showed statistically significant ($p < 0.01$) improvements in Aggressive Behavior Subscale scores of the Child Behavior Checklist, with large effect size (Cohen's d > 0.8).	Yes
Studies on general adolescent population.					
Bahrami et al. (2018)	Healthy adolescent females (M_{age} = 14.6 years, SD_{age} = 1.5 years)	940	Vitamin D: 1 capsule/week for a total of 9 weeks, contains 50,000 IU vitamin D. [9 weeks]	Intervention had no significant effect on Buss-Perry Aggression Questionnaire score (p = 0.188).	No
Hamazaki et al. (2008)	School children without any reported illnesses (~50 % males, $M_{age\ of\ intervention\ group}$ = 10.6 years, $SD_{age\ of\ intervention\ group}$ = 1.1 years, $M_{age\ of\ control\ group}$ = 10.6 years, $SD_{age\ of\ control\ group}$ = 1.0 years, $Range_{age}$ = 8–14 years)	189	DHA-rich oil: 6 fish oil capsules/day. 210 mg oil/capsule, containing 0.65 g DHA and 0.10 g EPA. [13 weeks]	No significant changes observed either over time or between intervention and control groups on the Buss-Perry Aggression Questionnaire, Physical Aggression Subscale scores (p-value and effect size not reported).	No
Itomura et al. (2005)	School children without any reported illnesses (~49 % males, $M_{age\ of\ intervention\ group}$ = 10.3 years, $SD_{age\ of\ intervention\ group}$ = 0.9 years, $M_{age\ of\ control\ group}$ = 10.4 years, $SD_{age\ of\ control\ group}$ = 0.9 years)	166	Fish oil-fortified foods containing 3600 mg of Docosahexaenoic Acid (DHA) and 840 mg of eicosapentaenoic acid (EPA) per week, through 2 pieces of bread rolls (1 bread roll = 300 mg DHA each), 2 pieces of steamed bread (1 steamed bread = 600 mg DHA), 3 sausages (1 sausage = 600 mg DHA) and spaghetti. [13 weeks]	A significant increase in aggression in the female control group (p = 0.0004) and no change in the female intervention group, with a significant intergroup difference (p = 0.008). There were no significant changes over time in boys. The changes in physical aggression scores over time and DEPA/AA ratio were significantly correlated in girls.	Mixed
Raine et al. (2015)	General adolescent population without any reported conditions (52 % males, $M_{age\ of\ intervention\ group}$ = 11.1 years, $SD_{age\ of\ intervention\ group}$ = 2.2 years, $M_{age\ of\ control\ group}$	200	Omega-3 supplementation (Smartfish Recharge): 1 g per day of omega-3 (300 mg of DHA, 200 mg of EPA, 400 mg of alpha-linolenic acid, and 100 mg of DPA) given in a 200 ml fruit-flavored drink.	At the end of treatment (6 months), there was no significant within-group difference in intervention group on the Child Behavior Checklist (CBCL); no significant within-group difference in	Mixed

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Table 3 (*continued*)

Study	Sample	N	Supplement [duration of supplementation]	Results	Treatment benefit
	= 11.6 years, $SD_{age\ of\ control\ group}$ = 2.1 years, $Range_{age}$ = 8–16 years)		Subjects consumed 6.54 ± 0.88 drinks per week. For detailed content of product, see study description in Supplementary Table 2. [26 weeks]	intervention group for Youth Self Report (YSR); and a significant decrease in intervention group ($p < 0.05$) on the Reactive Proactive Aggression Questionnaire (RPQ) child-report and parent-report ($p < 0.05$). At 6 months post-treatment, there was a significant group x time interaction favoring intervention group ($p < 0.01$, eta squared = 0.03) for the CBCL; no significant group x time interaction (eta squared<0.01) for the YSR; a significant group x time interaction favoring intervention group ($p < 0.01$, eta squared = 0.04) for the RPQ child-report; no significant group x time interaction (eta squared = 0.01) for the RPQ parent-report.	

relation to nutritional supplementation. Outcomes where no beneficial treatment effects were observed, included family-, cognitive-, general emotional-, and behavioral functioning, ADHD symptomatology, and internalizing behaviors. Finally, two studies did not report on any outcomes beyond those assessing aggression.

In terms of side effects, a slight majority of the studies (n = 12) monitored side effects of the nutritional supplements, while authors of 10 studies did not collect such data. Side effects were reported in 7 of the 12 studies and in each case, these occurred in a minority of participants, were minor or moderate in severity, and typically included nausea, change in bowel movement frequency, vomiting, or headaches. Detailed information on side effects for each study can be found in Supplementary Table 3.

4. Discussion

4.1. Interpretation of the results

The aim of the present study was to review the extant empirical data on the effectiveness of nutritional supplementation in reducing pathological hetero-aggressive behaviors in children and youth. Most studies investigated the effectiveness of essential fatty acids (with inconsistent outcomes). However, the evidence for a positive effect was most consistent for products containing a broad range of vitamins and minerals only (Fig. 2): all four studies (two randomized controlled trials and two uncontrolled pre-post studies) investigating such supplements showed treatment benefit These latter results overall suggest that there may be a role for broad-range multinutrient supplements in the management of aggression in youth and children; however, additional studies are needed to provide further support for this recommendation due to the low number of randomized controlled trials focusing on these supplements.

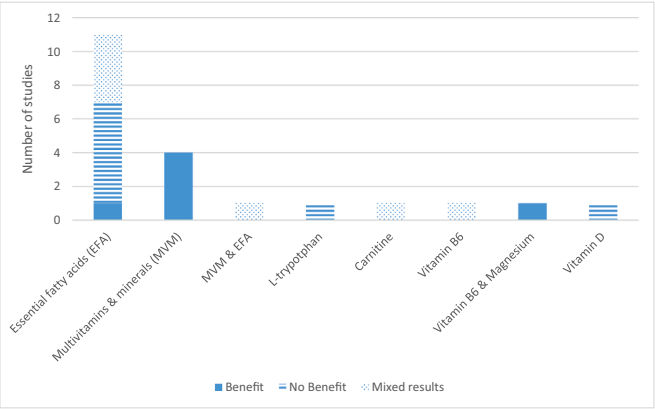

Fig. 2. Summary of main study outcomes (in terms of reducing child/youth aggression) by supplement type
Note. The study of Walsh et al., 2004 used an individualized number and combination of nutrients; therefore, the outcome of that study was not included in the figure.

The findings, favoring multinutrients in relation to their effectiveness to reduce aggression in children and youth, are in line with outcomes found in other areas on nutritional psychiatry, where complex formulas of vitamins and minerals proved to be effective in supporting different areas of mental health such as mood, posttraumatic stress, or non-aggression-related ADHD symptoms (Johnstone et al., 2020; Rucklidge & Kaplan, 2013; Sarris et al., 2015). The fact that broad-range micronutrient formulas seem to enhance not just one but multiple aspects of mental health without significant side effects make them a reasonable treatment alternative, especially for clients refusing conventional psychiatric medications or who have difficulties tolerating their side effects.

The consistently reported benefits of broad-range micronutrients found in this review are also in line with recent theoretical developments in nutritional psychiatry, emphasizing that healthy brain development and functioning is dependent on the simultaneous availability of a large variety of nutrients. This *simultaneous availability* enables metabolic and mitochondrial processes in the brain as well as regulating gene expression by methylation or supporting anti-inflammatory processes and the neutralization of neurotoxins (Rucklidge et al., 2021). Accordingly, supplementation with broad-range micronutrient formulas might help positively influence various dysfunctional neurobiological processes or states, that increase the likelihood of aggression, from the high level of certain aggression-inducing toxins (e.g., lead) through the low level of neurotransmitters necessary for appropriate inhibitory control (e.g., serotonin) to suboptimal microbiota development, composition, and metabolism.

4.2. Limitations

Results of the present study should be interpreted in light of certain limitations. First, both the electronic searches and the screening were completed by a single author, decreasing the reliability of these processes. In addition, the present work focused exclusively on nutritional supplements and did not consider the role diet might play in the regulation of aggressive behaviors. While the authors of the present study decided to focus on nutritional supplements considering the difficulties routinely described in relation to long-term adherence to dietary interventions (Desroches et al., 2013; Gibson & Sainsbury, 2017), it is important to acknowledge that modifying dietary habits both in terms of

food consumption and elimination may also have a role in reducing aggressive and antisocial behaviors (Benton, 2007).

Further, when making a decision on whether to consider a study sample as an adult or minor sample, we used the age of 18 as the threshold. While considering this particular age as the entry into adulthood is quite common across countries and settings, this decision is somewhat arbitrary and debatable. For instance, one could reasonably argue that in the context of nutrition and brain functioning, the true cut-off value should be the age when maturation of the brain is complete (i.e., the early twenties); or the contrary: that adolescents should already be considered as adults in this context due to their significant differences from younger children. However, the practical implications of this issue are minor as the evidence on individuals older than 18 years of age has recently been synthesized (Qureshi et al., 2021).

An additional limitation of the present review comes from the large diversity in the original studies in terms of sample characteristics, supplement type, study design and the consideration of pre-intervention nutrition levels—preventing the authors from conducting a quantitative synthesis (meta-analysis) of the results. Further, while the consideration of data from different study designs is necessary and beneficial when aiming to establish real-life effectiveness (Kaplan et al., 2011), simply pooling (cf. vote counting used in the present review) results of diverse studies when the number of studies is low and when they are heterogeneous in many regards (e.g., a pre-post study with a sample size of nine collapsed with a randomized controlled trial of several dozens of participants) carries significant risk of bias. However, we argue that evaluating the relatively few and heterogeneous existing data is helpful in preliminarily informing clinical practice and orienting future research.

4.3. Future directions

In terms of methodological features, included studies most often reported only on probability values when analyzing differences between two groups and were less likely to include estimates of effect size limiting the clinical utility of the findings. Moreover, authors sometimes failed to report even probability values if those were deemed as not significant, which along with low statistical power made the results more difficult to interpret. Therefore, in line with general recommendations on effectiveness / efficacy research (Wilkinson, 1999), we encourage future authors to consistently report effects sizes and address the issue of type II error either through a priori power analysis and/or alternative post hoc analyses (Lakens, 2017) to better inform clinical decision making. Collecting and interpreting data on the successfulness of blinding would also improve the quality of randomized trials in this field (none of the studies included in the evidence synthesis did so).[1]

Different forms (e.g., hetero- versus auto-; reactive versus proactive) of aggression may have different neuroanatomical and neurophysiological correlates and mechanisms of action (Shiina, 2015; Waltes et al., 2016), which in turn might respond to nutritional status and nutritional interventions differently. Therefore, given this inherent heterogeneity within the construct of aggression, future studies in the field should clearly define (during the design phase of the study) and report (during the dissemination of the results), which type of aggression is studied. We also encourage future authors of the field that they systematically investigate not just supplement content but dosage as well (and provide a justification for their choice), ideally in the context of dietary habits. It is possible that some of the current, non-significant findings are more related to inappropriate dosing or heterogeneity of participants' baseline dietary intake than ineffective nutrient content, which deserves further study.

This latter possibility is also related to a more general inconsistency in the field, that of the necessity of pre-intervention nutrition level assessments. While some authors argue that nutritional supplementation should only be given to those displaying a measurable 'absolute' deficiency (e.g., Schoenthaler et al., 1997), others argue that this is not feasible (e.g., Rucklidge et al., 2021). The former group of experts argue that aggression of participants who were treatment-responders related to suboptimal pre-intervention nutrient levels, while proponents of the latter notion point out that due to the idiosyncrasy of individuals' nutritional needs (cf. the influence or stress, specific metabolic or gut microbiota characteristics etc.), our current, relatively simplistic assessment protocols for nutrient levels are not necessarily helpful in determining who might benefit from nutrient supplementation. Considering the practical importance of this question, future studies should systematically collect information on whether pre-intervention nutritional assessment is helpful in predicting treatment response.

We also make note that the duration of supplementation needed to reach *and* sustain beneficial mental health effects needs to be clarified. The relatively few longer term studies in nutritional psychiatry indicate that best outcomes emerge if clients continue to take their nutrient supplements for a year or even longer (Darling et al., 2019; Mehl-Madrona & Mainguy, 2017; Rucklidge et al., 2017), in which case, studies with 2–4 months of supplementation are only preliminary informative (cf. the mean supplementation duration in the studies reviewed here was 14.8 weeks with a median of 13 weeks). Further, some studies investigated the outcome variables after supplementation was discontinued, which might make more sense from a standard medication effectiveness perspective but seems less consistent with a nutritional approach, which is based on the assumption that the supplemented nutrients are needed on a long-term basis for the healthy development and functioning of the central nervous system.

5. Conclusion

Correction of absolute or relative nutritional deficiencies in children might have beneficial effects on present and future physical and mental health. Nutritional supplements are cheaper on the system level than conventional mental health treatment (Kaplan et al., 2017) and more affordable for individuals than most psychological interventions; further, they are also more widely accepted by parents and have a more positive side effect profile than most psychotropic medications (Zaalberg, 2019). To identify those nutritional supplements that offer the most benefit for reducing excessive hetero-aggression in children and youth, we have evaluated the empirical data accumulated to date. This systematic review concluded that while the data are still inconsistent regarding the benefits of essential fatty acid supplementation and insufficient regarding most other supplements investigated to date, findings in relation to broad-range vitamin and mineral supplements point into the direction that such products may have a role in the management of aggression. Their consideration seems warranted especially when bearing in mind the wide range of other (mental) health benefits broad-range micronutrient supplements could provide beyond the regulation of violent behavior, with very minor side effects (Johnstone et al., 2020; Johnstone et al., 2022; Rucklidge et al., 2018; Rucklidge et al., 2021). However, further high-quality, appropriately powered trials are definitely needed to provide further support to the above recommendation.

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[1] The study of Schoenthaler and Bier (2000) as well as Itomura et al. (2005) mention that the authors made attempts to assess the success of the blinding process but they do not describe the outcomes of these assessments.

Declaration of competing interest

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

Data availability

No data was used for the research described in the article.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.avb.2023.101841.

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