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Omega-3/6 Fatty Acids and Learning in Children and Young People: A Review of Randomised Controlled Trials Published in the Last 5 Years

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Abstract

Helping children to learn and focus is a central part of educational pedagogy. Given that the human brain is around 60 per cent fat the present review sets out to evaluate the role of omega-3/6 fatty acids in relation to aspects of classroom learning. This is particularly relevant in modern day given that there has been a shift in children's fatty acids profiles, with movement towards an increased ratio of omega-6 to 3. Using the National Centre for Biotechnology Information PubMed database, a search was made for all studies published between 2012 and 2017 that met defined inclusion criteria. A total of 29 Randomised Controlled Trials (RCT) were identified which used Omega 3/6 fatty acids as interventions. Twenty-two studies (n=3,336) showed overall benefits, ranging from improvements in blood fatty acid levels to improved sleep. Eight trials (n=768) recruiting children and young people with ADHD at baseline reported specific improvements in ADHD symptoms. Six studies (n=1092) showed that omega 3/6 fatty acids can support learning (improved reading ability, spelling, behaviour, attention and reduced hyperactivity and aggression). Strongest benefits are seen amongst those with: 1) ADHD or comorbid learning conditions, 2) suboptimal omega-3 status or 3) who underperform at baseline. RCTs focusing on vulnerable groups such as Looked After Children (LAC) and those with specific learning difficulties such as dyslexia and dyscalculia who could also potentially benefit from omega-3/6 fatty acids warrant further investigation.

Keywords: Omega 3/6 fatty acids; Learning; ADHD; Children; Attention; Behaviour

Abbreviations: ADHD: Attention Deficit Hyperactivity Disorder; ALA: Alpha-linolenic Acid; ARA: Arachidonic Acid; ASD: Autistic Spectrum Disorder; DHA- Docosahexaenoic Acid; EPA: Eicosapentaenoic Acid; GLA: Gamma Linoleic Acid; MPH: Methylphenidate; PS: Phosphatidylserine; PUFA: Polyunsaturated Fatty Acids; RCTs: Randomised Controlled Trials; TS: Tourette Syndrome.

Introduction

There is increasing evidence that nutritional insufficiencies, including that of omega-3 fatty acids can have adverse effects on brain development and neurodevelopment [1], thereby impacting on the ability to learn to and function sociably. It is well documented that humans once evolved on a diet providing a balanced 1:1 ratio of omega-6 to omega-3 fatty acids which is important for normal development throughout the life span [2]. Yet Western diets now have a ratio of omega-6 to omega-3 of 10:1 up to 20-25:1 – a profile distinctly different to that on which humans evolved and their genetic patterns were established [2].

Typically, the human brain is around 60 per cent fat [3] with the omega-3 fatty acid docosahexaenoic acid (DHA) being abundant in the brain and its neuronal membranes where it supports normal neurological function [4]. Equally, scientific literature implies that the evolution of the higher order of brain function in humans was once attributed to our omega-3 and DHA intakes, with DHA found to be densely accumulated in areas of the brain associated with learning and memory [5]. Concerns have been raised that modern diets lacking in omega-3 fatty acids may have adverse effects on a child's learning, reading, and attention [6]. These links are not surprising given that brain cell membranes are rich in phospholipids composed of these fatty acids, with evidence that these facilitate transport across the membranes and modulate neurotransmitter systems [4,7,8].

Current evidence suggests that omega-3 status, especially DHA, may enhance cognitive performance including aspects of learning, memory and speed of performing cognitive tasks and children whose diets are low in these may benefit the most [9]. For example, Italian research has shown that children's blood omega-3 levels tend to be highest in neonates (new-borns) and lowest in children, especially that of DHA indicating a decline from birth and that dietary intakes are generally inadequate [10]. An Oxfordshire cross-sectional evaluation of schoolchildren aged 7 to 9 years (n=493) showed that low DHA blood concentrations were associated with reduced reading ability, working memory and higher levels of parent-related oppositional behaviour and emotional liability [11]. Similarly, a UK study of 13 to 16-year-old teenagers (n=196) found omega-3 status to be low at baseline [12]. Other work comprised of boys aged 6 to 12 years observed that there were a greater number of behavioural problems including temper tantrums and sleeping problems amongst those with lower omega-3 fatty acids levels [13].

Amongst children with a history of school failure the prevalence of learning difficulties and developmental disorders, including dyslexia and dyscalculia has been reported to be 32 per cent (6.4 per cent in the general population) [14]. Dyslexia is the most common learning disability and is known to have multifactorial causes with defects in highly unsaturated fatty acid metabolism thought to be one possible underpinning factor [15]. In children with Attention Deficit

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Hyperactivity Disorder (ADHD), omega-3 levels have been shown to be lower compared with controls [16,17]. For example, one assessment using blood samples from 565 children aged 3 to 17 years found that children with Attention Deficit Hyperactivity Disorder (ADHD) and Autistic Spectrum Disorder (ASD) had low levels of EPA, DHA and arachidonic acid (ARA) and higher ratio of n-6/n-3 which corresponded with their symptoms [18]. A meta-analysis (based on 10 studies) concluded that omega-3 levels may contribute to reducing emotional lability and oppositional behaviour in subgroups of children with ADHD [17].

Unfortunately, children who move around the system may have a poor omega-3 status such as those in care (Looked After Children). They also have far higher rates of learning difficulties. The two factors may be linked. Greater knowledge and attention to their nutritional status could help to place them on a more positive path earlier on in life [19]. This may be particularly important if we consider the impact of early childhood adversity as childhood omega-3 status also tracks back to the periconceptual period with low DHA and ALA intakes in pregnancy and lactation correlating with infant and childhood fatty acid status [20,21].

Unlike most other developmental disorders ADHD is treated with medication along with psychological interventions. ADHD is a complex condition where performance on cognitive tasks is reduced compared with neurotypical individuals [22]. Presently, in the USA alone the economic burden of ADHD due to medication costs is estimated to be 77 billion dollars [23]. Typically, methylphenidate (MPH) is the first-line pharmacological treatment for ADHD. However, side effects such as sleep disturbances, growth and appetite reduction are reported for some children [24]. Whilst traditional stimulant medications have a role to play in ADHD management there have been concerns about their long-term use amongst children with ADHD [24-26].

Taken together, the present paper sets out to evaluate the role of omega-3/6 fatty acids in relation to aspects of learning in children and young people, particularly in the context of ADHD management.

Methods

The National Centre for Biotechnology Information (NCBI) search engine (PubMed) and Rayyan software used to create systematic reviews [27] were used to extract relevant publications. For inclusion, studies were undertaken during the last 5 years (January 2012 to September 2017). All publications were English-language human randomised controlled trials conducted on children or young people aged 3 to 18 years. Recent evidence has shown that the identity of omega-3 can successfully be blinded to participants [28]. Articles were excluded if they were published before 2012 or a pilot study.

Key search terms included omega-3 and omega-6 fatty acids combined with 'attention deficit hyperactivity disorder', 'autism spectrum disorder', 'developmental coordination disorder' (including brain dysfunction), 'cognition', 'attention' (including concentration and disruptive behaviour), 'learning', 'literacy', 'reading', 'spelling' word blindness, dyslexia and dyspraxia) and 'behaviour'. The search focused on 'children' and 'young people' which included those who were looked after or institutionalised.

Data files extracted from the NCBI collection depository and Rayyan software were evaluated with the following being collated: 1) Author and country of research, 2) Subjects (number of participants, gender, baseline health and conditions), 3) Mean age, 4) Study design and methods, 5) Type and dose of supplements and 6) Main findings (Table 1).

Results

The NCBI and Rayyan Systematic Reviews software search identified 31 papers meeting the outlined criteria. A total of 1192 publications using the specified search terms were identified [27]. Once the RCT criteria was applied a further 1111 studies were excluded. A

Author (year) Country	Subjects M/F, sample size	Mean age	Study design and methods	Type & dose of supplement	Main findings
ADHD					
Assareh et al. [51]	n=40 with ADHD	6-12 years	10-week DB RCT.	Treatment group received MPH + DHA, EPA & omega-6. Control group received a placebo + MPH.	Results did not support the efficacy of PUFA in the treatment of ADHD,
Barragan et al. [25]	n=90 with ADHD	6-12 years Mean age 8.27 years	12-month trial (unblinded); MPH, omega-3/6 or a combination	Equazen: 558 mg EPA, 174 mg DHA, and 60 mg GLA (9:3:1 ratio)	Significantly better scores on ADHD. Total and hyperactivity-impulsivity subscales with omega + MPH compared with omega-3/6 alone. Adverse events were numerically less frequent with omega-3/6 or MPH + omega-3/6 than MPH alone.
Anand et al. [31]	n=50 with ADHD	4-11 years	4-month DB RCT.	The control group was given Atomoxetine. The study group was given Atomoxetine + 180 mg of EPA & 120 mg of DHA.	The study group had greater reduction in ADHD scores as compared to the control group, although not statistically significant (p=0.08).
Bos et al. [32]	40 M with ADHD and 39 without ADHD	8-14 years	16-week DB PC trial.	10 g of margarine daily, enriched with either 650 mg of EPA/DHA each or placebo.	Omega-3 fatty supplementation reduced symptoms of ADHD, both for individuals with ADHD and typically developing children. This effect did not appear to be mediated by cognitive control systems in the brain, as no effect of supplementation was found here.

Matsudaira et al. [50]	76 M with ADHD	12-16 years. mean=13.7	12-week RCT.	Equazen: Six capsules daily provided 558 mg EPA and 174 mg DHA, 60 mg of omega-6 fatty acid γ-linoleic acid and 9.6 mg vitamin E.	No superiority of LCPUFA to placebo was observed on the primary outcome (p=0.671). Future studies should use larger sample sizes and longer supplementation periods.
Milte et al. [29]	90 with ADHD	NR	4-month RCS.	Allocated to consume supplements high in EPA, DHA, or linoleic acid (control).	Increased erythrocyte EPA + DHA was associated with improved spelling (p<00.001), attention (p<00.001), reduced oppositional behaviour (p<0.003), hyperactivity (p<0.001), cognitive problems (p < 0.001), DSM-IV hyperactivity p=0.002) and DSM-IV inattention (p<0.001).
Wu et al. [33]	179 with lower IQs or ADHD	School age children	3-month trial.	Received ordinary eggs (n=90) or eggs rich in C18:3 ω-3, EPA, 20:5 ω-3 and DHA, 22:6 ω-3 (n=89)	Visual acuity in the study group was significantly better than that of the control group (p=0.013). Dietary supplementation with omega-3 PUFAs improved visual acuity and the RBC fatty acid profile in school-age children with lower IQs or ADHD.
Widenhorn-Müller et al. [34]	95 with ADHD	6-12 years.	16-week DB PC trial.	(no dosage info)	Supplementation with the omega-3 fatty acid mix increased EPA and DHA concentrations in erythrocyte membranes and improved working memory function, but had no effect on other cognitive measures and parent- and teacher-rated behavior in the study population.
Manor et al. [35]	200 with ADHD	NR	15-week DB PC trial.	Phase 1=300 mg PS-Omega3/day Phase 2=150 mg PS-Omega3/day	Study results showed that consumption of phosphatidylserine-omega3 by children with ADHD is safe and well tolerated (over 30-week period), without any negative effect on body weight or growth.
Hariri et al. [36]	103 with ADHD	6-12 years	8-week DB trial.	The n-3 group received n-3 fatty acids (635 mg eicosapentaenoic acid (EPA), 195 mg docosahexaenoic acid (DHA).	8-weeks of EPA and DHA supplementation decreased plasma inflammatory mediators and oxidative stress in the children with ADHD. These results suggest that n-3 fatty acid supplementation may offer a safe and efficacious treatment for children with ADHD.
Johnson et al. [40]	75 with ADHD	8-18 years	3-month RCT.	Equazen: 558 mg EPA, 174 mg DHA, and 60 mg gamma linoleic acid (9:3:1 ratio) or placebo.	Omega 3/6 supplementation had a clear impact on fatty acid composition in the active versus placebo group, and the fatty acid changes appear to be associated with treatment response in children with ADHD.
Manor et al. [41]	200 with ADHD	No age info	15-week DB PC trial.	PS-Omega3 or placebo.	Phosphatidylserine omega-3 may reduce ADHD symptoms in children. This treatment may be especially effective in a subgroup of hyperactive-impulsive, emotionally and behaviourally-dysregulated ADHD children.
Milte et al. [30]	90 with ADHD.	7-12 years	4-month RCT.	Participants consumed 4 × 500-mg capsules per day containing an EPA-rich fish oil providing EPA 1109 mg and DHA 108 mg, a DHA-rich fish oil providing EPA 264 mg and DHA 1032 mg, or a safflower oil (control) providing LA 1467 mg/d.	Erythrocyte FA profiles showed that increased erythrocyte omega-3 PUFA, specifically DHA, may improve literacy and behavior in children with ADHD. The greatest benefit may be observed in children who have comorbid learning difficulties.

Perera et al. [42]	Children with ADHD n=48 active group, n=46 placebo	6-12 years	6-month trial	Capsule containing n3 and n6 (fish oil) and cold-pressed evening primrose oil.	Statistically significant improvement was not found at 3 months of treatment between groups but was evident at 6 months of treatment (p<0.05) with inattention, impulsiveness, and cooperation with parents and teachers.
ASD and other conditions					
Bent et al. [37]	57 with autism	5-8 years	A novel, Internet-based clinical trial design to evaluate the efficacy of omega-3 fatty acids.	1.3 grams of omega-3 fatty acids or an identical placebo daily for 6 weeks	Children in the omega-3 fatty acid group had a greater reduction in hyperactivity (-5.3 points) compared to the placebo group (-2.6 points), but the difference was not statistically significant.
Voigt et al. [53]	48 with autism	3-10 years	6-month DB randomised trial	200 mg of DHA or a placebo.	Dietary DHA supplementation of 200 mg/day for 6 months did not improve the core symptoms of autism. Results may have been limited by inadequate sample size.
Gabbay et al. [38]	33 with Tourette's disorder.	6-18 years	20-week DB PC trial.	In all capsules, 20% of the mass was the inert capsule. Of the remaining 80% 65% was omega-3 FA, with an EPA: DHA ratio of 2:1 (250 mg or 500 mg of EPA+DHA per capsule).	Omega-3 FA did not reduce tic scores but may be beneficial in reduction of tic-related impairment for some children and adolescents with Tourette's disorder.
Cognition					
Bauer et al. [56]	NR	Young adults	30-day DB counterbalanced, crossover study.	No dosage info.	DHA-rich supplementation was less effective than EPA-rich supplementation in enhancing neurocognitive functioning after a 30-day supplementation period.
Portillo-Reyes et al. [39]	59	8-12 years	3-month DB PC clinical trial.	No dosage info	More than 50% of children in the treatment group had greater improvement in 11 of the 18 neuropsychological variables studied. Processing speed, visual-motor coordination, perceptual integration, attention and executive function showed improvement in more than 70% of the omega-3 supplemented children.
Benton et al. [57]	285	Young adult females	50-day DB PC trial.	400 mg of DHA or placebo.	After 50 d, recently acquired information was more likely to be forgotten by those who had consumed DHA.
Baumgartner et al. [58]	321 with poor iron and n-3 status	6-11 years	8.5 month 2-by-2 factorial trial.	1) iron (50 mg) plus DHA/ EPA (420/80 mg), 2) iron plus placebo, 3) placebo plus a mixture of DHA and EPA (DHA/EPA), or 4) placebo plus placebo as oral supplements (4/week)	DHA/EPA supplementation had no benefits on cognition and impaired working memory in anaemic children and long-term memory and retrieval in girls with ID.
Kirby et al. [43]	450 mainstream school.	8-10 years	16-week DB PC RCT.	Active supplements (containing DHA & EPA) or a placebo	After supplementation, changes in the relationship between omega-6 and omega-3 were significant in the active group. Only three significant differences between groups were found after 16 weeks, one of which was in favour of the placebo condition.
Educative outcomes and behaviour					
Johnson et al. [6]	154 mainstream children	9-10 years	3-month parallel DB PC randomized trial followed by 3-month active treatment.	Equazen: Three Omega 3/6 capsules twice daily (558 mg EPA, 174 mg DHA, and 60 mg GLA) or placebo capsules (palm oil). In Study Period 2 (from 3 to 6 months), all subjects received open-label active treatment.	Compared with placebo, 3 months of Omega 3/6 treatment improved reading ability - specifically the clinically relevant 'phonologic decoding time' and 'visual analysis time' - in mainstream schoolchildren. In particular, children with attention problems showed treatment benefits.

Tammam et al. [12]	196 typically developing children	13-16 years	12-week DB PC trial	Vitamin, mineral & n-3 supplementation	The children's LCPUFA (n-3 and n-6) improved significantly in the group treated (p=0.0005). On the Conners' disruptive behaviour scale, the group given the active supplements improved, whereas the placebo group worsened (p=0.02).
Milte et al. [29]	90 with ADHD	NR	4-month RCS.	Allocated to consume supplements high in EPA, DHA, or linoleic acid (control).	Increased erythrocyte EPA + DHA was associated with improved spelling (p<0.001), attention (p<0.001), reduced oppositional behaviour (p<0.003), hyperactivity (p<0.001), cognitive problems (p<0.001), DSM-IV hyperactivity p=0.002) and DSM-IV inattention (p<0.001).
Milte et al. [30]	90 with ADHD.	7-12 years	4-month RCT.	Participants consumed 4 × 500-mg capsules per day containing an EPA-rich fish oil providing EPA 1109 mg and DHA 108 mg, a DHA-rich fish oil providing EPA 264 mg and DHA 1032 mg, or a safflower oil (control) providing LA 1467 mg/d.	Erythrocyte FA profiles showed that increased erythrocyte omega-3 PUFA, specifically DHA, may improve literacy and behavior in children with ADHD. The greatest benefit may be observed in children who have comorbid learning difficulties.
Raine et al. [44]	200 children from the community	8-16 years	6-month randomized DB PC stratified, parallel-group trial.	Supplementation consisted of a fruit drink containing 1 g/day of omega-3 or a placebo consisting of the same fruit drink without omega-3.	Parents whose children took omega-3 showed significant posttreatment reductions in their own antisocial and aggressive behaviour.
Richardson et al. [45]	362 underperforming in reading	7-9 years	16-week intervention.	600 mg/day DHA (from algal oil), or taste/colour matched corn/soybean oil placebo.	Parent-rated behaviour problems (ADHD- symptoms) were significantly reduced by active treatment, but little or no effects were seen for either teacher-rated behaviour or working memory.
Other.					
Arnold et al. [46]	n=95	7–14 years	12-week PC 2 x 2 trial.	12 weeks of O3 supplementation (1.4 g EPA, 0.2 g DHA and 0.27 g other omega 3 per day; PEP; their combination; or placebo	Compared to placebo, 2 gO3 per day increased EPA blood levels sevenfold and DHA levels by half (p<0.001). Body weight correlated inversely with increased EPA (p=0.004) and DHA (p=0.003) and positively with clinical mood response.
Christian et al. [48]	64 youth with a diagnosed mood disorder	7-14 years	12-week DB RCT.	Youth randomized to ω-3 received two 500 mg ω-3 capsules (350 mg EPA, 50 mg DHA; 100 mg other ω-3) twice daily =total daily dose of 2000 mg of ω-3 (1400 mg EPA, 200 mg DHA; 400 mg other) or allocated to a control.	In the ω-3 supplementation group, higher baseline body weight predicted less plasma accumulation of both EPA [p=0.003] and DHA [p=0.004]. Given increasing variability in weight within BMI percentile ranges as youth age, dosing based on absolute weight should be considered.
Montgomery et al. [47]	395	7-9 years	16-week RCT on healthy children from mainstream UK schools.	600 mg day with algal DHA versus placebo	The treatment trial showed no significant effects on subjective sleep measures. However, in al subsample, DHA supplementation led on average to seven fewer wake episodes and 58 min more sleep per night.

Key: DB- Double-Blind; DSM- Diagnostic and Statistical Manual of Mental Disorders; BMI- Body Mass Index; NR- Not Reported; DHA- Docosahexaenoic Acid; EPA- Eicosapentaenoic Acid; F- Female; FA- Fatty Acids; GLA- Gamma-Linolenic Acid; ID- Iron Deficiency; LC- Long-Chain; M- Male; MPH- Methylphenidate; PUFA- Polyunsaturated Fatty Acid; RCS- Randomised Crossover Study; RCT- Randomised Controlled Trial; PC- Placebo-Controlled; PS- Phosphatidylserine; PEP- Psychoeducational Psychotherapy.

Table 1: Omega 3/6 fatty acids and aspects of learning.

further 48 studies were removed as the abstract was not written in English language. This left 33 studies meeting the systematic review criteria. Further evaluation of abstracts identified one pilot trial and one methodological review. Subsequently, a further 2 publications were excluded leaving 31 RCTs in the final analysis. Two of these papers were replicas but have been included as different aspects of the papers related to different two outcomes screened – ADHD and educative outcomes [29,30]. Subsequently, the sample size projections were equated from 29 studies.

The algorithm of the qualifying publications is shown in Figure 1. Of these, six studies were conducted in the UK, four in Europe, six in the USA, three in Australasia, three in Mexico, two in Asia, two in Israel, two in Iran and one in India. Twenty-two studies (n=3,336) showed overall benefits, ranging from improvements in blood fatty acid levels to improved sleep (Table 1) [6,12,25,29-48].

ADHD

Amongst those with ADHD learning difficulties and disabilities are typically present whilst hyperactivity may or may not occur [49]. Fourteen RCTs recruited children or young people with ADHD at baseline. The age range of children and young people included extended was from 4-18 years (Table 1). One trial focused on the safety of phosphatidylserine (PS) enriched with 300 mg omega-3 fatty acids (namely EPA) finding that this was safe and well tolerated when taken by children with ADHD for up to 30 weeks [35].

Over half of the trials (8 studies) focusing on ADHD reported general benefits in symptoms [25,29-32,40-42]. Three studies provided a 9:3:1 ratio of fatty acids (558 mg EPA, 174 mg DHA and 60 mg GLA; Equazen) with two showing notable improvements in ADHD scores [25] and blood fatty acid composition which correlated with improved ADHD symptoms (defined as responders) [40]. In terms of broader aspects of learning improved attention, spelling and reduced oppositional behaviour were evident amongst 53 Australian children (n=53) taking EPA, DHA and LA supplements over 4-months [29].

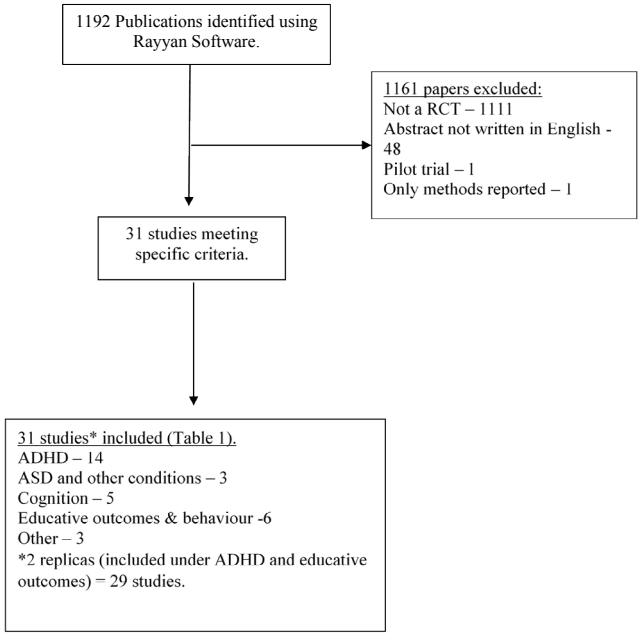

Figure 1: Algorithm for identifying trials.

Similarly, another 4-month trial found that omega-3 supplementation (particularly DHA) improved ADHD symptoms along with word reading, spelling, the ability to divide attention, reduced parent-rated oppositional behaviour, hyperactivity and restlessness in children with ADHD and comorbid learning difficulties [30]. Other studies showed that PS-omega-3 when taken over 30 weeks reduced children's ADHD symptoms with effects being more prominent amongst those with hyperactivity-impulsivity, emotionally and behaviourally-dysregulated ADHD [41].

With regard to adjunctive roles, in one 12-month randomised study of 90 children taking either omega-3/6 fatty acids (the ratio was 9:3:1 EPA; DHA: GLA; Equazen), MPH or a combination found that ADHD symptoms reduced significantly amongst those taking omega-3/6 and MPH whilst Clinical Global Impressions–Severity (CGI-S) scale scores (a measure of symptom severity) decreased slowly and consistently amongst the omega-3/6 group [25]. In another study where ADHD children were being treated with MPH, they were allocated to take a capsule containing omega 3 and 6 fatty acids over 6 months. Statistically significant improvements were noted at 6-months in attention, cooperation with teachers and parents and impulsivity with reporting's of academic performance, completion of work, restlessness and aggressiveness was also found to improve [42]. A smaller 4-week RCT comprised of 50 Indian children with ADHD noticed that those taking Atomoxetine along with 180 mg EPA and 120 mg DHA had reduced ADHD scores (along with inattention and hyperactivity) particularly in the combined type of ADHD [31].

Two studies looked at foods as a vehicle for omega-3/6 delivery. Amongst 174 Chinese children with ADHD (and lower IQs) eggs enriched with EPA and DHA over three months improved erythrocyte fatty acid profile and visual acuity [33]. A 16-week study recruiting just boys found that daily margarine consumption providing 650 mg EPA/DHA reduced ADHD symptoms and parent-rated attention in children with ADHD and typically developing children alike [32].

Other studies report more generic benefits. For example, an Iranian double-blind trial consisting of 103 children found that 635 mg EPA and 195 mg DHA reduced markers of oxidative stress and inflammation when taken over 8 weeks [36]. Other German research comprised of 95 six to 12-year olds showed that an omega-3 fatty acid mix taken daily over 16-weeks improved EPA and DHA erythrocyte levels and children's working memory [34].

Some studies reported limited effects. A 12-week trial consisting of 76 male adolescents with ADHD allocated to omega-3/6 fatty acids or a placebo did not observe any significant effects in the Conner's Teacher Rating Scale, aggression, impulsivity, depression, or anxiety [50]. A small Iranian trial (n=40) did not support the efficacy of PUFA in ADHD although reductions in Parent ADHD Rating Scale Scores (for impulsivity) were significantly higher in the PUFA group after adjustment for the effect of age, sex, and dose of methylphenidate [51].

ASD and other conditions

Autism Spectrum Disorders (ASD) impact considerably on learning and communication that can affect around 1% of children (USA data) [52]. To date three studies have investigated the effects of omega-3/6 fatty acids in relation to ASD or other learning conditions.

In an internet-based RCT five to eight-year olds (n=57) with autism taking 1.3 g of omega-3 fatty acids daily over 6 weeks had reduced hyperactivity compared with the placebo group, although this was not statistically significant [37]. A similar sized trial tested the effects

of DHA supplementation (200 mg/d over 6 months) on the main symptoms of ASD amongst three to 10 years olds (n=48). Whilst those receiving the supplementation experienced a 431% median increase in plasma DHA levels no statistically significant effects on the main symptoms of ASD were observed [53].

Tourette syndrome (TS) is another common neuropsychiatric disorder in children where motor and vocal tics are presented which can vary in severity [54]. A recent double-blind RCT allocating 33 children with TS to either omega-3 fatty acids or an olive oil placebo over 20 weeks observed some benefits in relation to reduced tic-related impairment [38]. Unfortunately, the small sample size and olive oil placebo may have confounded the strength of these results.

Cognition

Amongst healthy school-aged children there is growing evidence that omega-3 fatty acids including DHA can have favourable roles on aspects of cognition or behaviour [55]. Five studies focused on omega-3/6 fatty acids and aspects of cognition, with varying effects. Amongst older malnourished Mexican children (8 to 12 years) 3-month omega-3 supplementation improved 11 out of the 18 neuropsychological variables studied in more than 50 per cent of children [39]. Alongside this processing speed, visual-motor coordination, attention and executive function improved in more than 70 per cent of the omega-3 supplemented children [39].

Amongst a UK sample of healthy mainstream children taking DHA/EPA over 16-weeks few cognitive effects were observed and one was in favour of the placebo group [43]. An Australian trial found DHA to be less effective than EPA (EPA appeared to help their brains work 'less hard') at improving neurocognition in young people after 30-days of supplementation [56]. One UK trial which recruited young adult females found that DHA supplementation (400 mg/day over 50-days) had no effects on cognitive enhancement [57]. Similarly, a Swiss trial involving anaemic children found that DHA/EPA did not help to improve cognition, working memory or memory retrieval [58].

Educative outcomes and behaviour

Six studies evaluated omega-3/6 fatty acids in relation to educative outcomes or aspects of behaviour. Amongst main school children a double-blind trial found that omega-3/6 supplementation improved 9-10 year olds reading ability – particularly clinically relevant 'phonologic decoding time' and 'visual analysis' time [6]. These findings were even more pertinent amongst children with attention problems who showed significant treatment benefits [6]. Another 12-week trial carried out on typically developing East End London teenagers aged 13 to 16 years found that disruptive behaviour improved in the active supplement (EPA and micronutrients) but declined in the placebo group [12]. One trial recruiting children from the community found that drinking a fruit beverage containing 1 g/day of omega-3 over 12 months led to significant post-treatment reductions in antisocial and aggressive behaviour [44].

In the UK DHA Oxford Learning and Behaviour (DOLAB) study an algal-derived DHA supplement taken over 16-weeks was found to improve reading in those who were initially underperforming (baseline reading performance ≤ 20th centile) and reduce parent-rated behaviour problems [45]. Two other trials recruited children with ADHD at baseline. For example, a randomized crossover trial observed that EPA, DHA and LA supplementation over 4-months significantly improved children's attention, spelling and oppositional behaviour whilst reducing hyperactivity [29]. Equally, earlier work by the same team of scientists found that omega-3 PUFA improved literacy and behaviour in 7-12 years old with ADHD [30].

Other

Three studies have looked at other effects of omega-3/6 fatty acids which could indirectly affect omega fatty acids status and ability to learn. For example, a recent 12-week RCT providing 7 to 14-year olds with omega-3/6 fatty acids showed that children with a higher body weight had lower levels of EPA and DHA accumulation indicating that dosing may need to be based on weight [48]. Similarly, another recent trial observed that supplementation with 2 g/day of omega-3 fatty acids substantially increased blood levels, more so in smaller children, implying a possible U-shaped curve in relation to bodyweight and omega response [46]. Increased EPA also correlated positively with children's clinical mood response [46].

A third trial focusing on sleeping patterns in healthy children aged 7 to 9 years discovered that providing algal DHA daily over 16 weeks was associated with on average of 7 fewer waking episodes and 58 minutes sleep more per night compared to the control [47].

Discussion

Latest evidence indicates that children of today have altered omega-3/6 fatty acids profiles with a tendency towards inadequate omega-3 status [10-13,59]. There are many underpinning reasons behind this. Low intake of oily fish is one with latest evidence showing that children aged 4 to 10 years eat just 2 g of oily fish daily (less than one-fifth of a portion per week) [60]. Equally, evidence from meta-analysis publications implies that fatty acids profiles are altered amongst children with ADHD and ASD with a tendency towards lower EPA, DHA and ARA levels and a higher ratio of omega-6 to 3 fatty acids, with a possible genetic aetiology underpinning this [16,17,42].

From the RCTs evaluated 8 trials found that omega-3/6 fatty acids may help to reduce ADHD symptoms in school-aged children and young people [25,29-32,40-42] which has the potential to assist them in the context of classroom learning. A growing body of evidence also suggests that omega-3/6 fatty acids have an adjunctive role to play, helping to lower the dose and compliance with ADHD medications such as MPH, particularly when taken in a 9:3:1 ratio of EPA to DHA and GLA [25,61]. For example, a combination of omega-3/6 with MPH has been found to permit lower doses of MPH (monotherapy, 1.0 mg/kg/day; combination, 0.8 mg/kg/day) [25]. A recent critical review paper concluded that two patient groups could benefit from omega-3 fatty acids: 1) Those with mild ADHD where these could replace stimulant treatments and 2) Those with severe ADHD or side effects from stimulant treatments where omega-3 fatty acids could reduce the amount of stimulant medication needed and resultant side-effects experienced [61]. Meta-analytical work has also demonstrated that omega-3 supplementation monotherapy can improve clinical symptoms and cognitive performance in children and teenagers with ADHD indicating that this may be a suitable treatment option [62]. Where studies yield inconsistent findings the dose and ratio of fatty acids should be considered alongside methodological rigour.

Benefits of omega-3/6 fatty are apparent in healthy mainstream children indicating an extended role for omega 3/6 supplementation, particularly in relation to improving aspects of literacy such as reading ability, phonological decoding time and visual analysis [6], behaviour [12] and antisocial tendencies [44]. In terms of underpinning mechanisms research using sustained attention tasks shows that omega-3/6 supplementation can increase in brain activation in the

prefrontal areas and improve task performance in both typically developing children and those with ADHD [56,63]. So, it seems that the effects of omega-3/6 fatty acids may involve attention networks rather than being mediated by dopaminergic cognitive control networks [32]. This may be one reason why there were some inconsistencies in findings amongst studies focusing on cognitive performance.

It is also evident that the role of omega-3/6 fatty acids appears to impact on other aspects of children and young people's health, such as their sleep [47] and mood [46]. A recent cross-sectional study has also shown that an elevated omega-6 to 3 ratio was associated with an increased risk of mood disorders in young people with an ultra-high risk (UHR) phenotype [64]. These areas, in particular, also warrant further observation and study. Body weight is another interesting area, with recent suggestions that tailored omega doses may be needed according to children's and young people's body weight [46,48].

Clearly, in order for the effects of omega-3/6 fatty acids to have clinically significant effects these need to be taken in a suitable ratio, dose and for a sufficient duration, ratio and in an adequate dose [31]. In several studies a 9:3:1 ratio of EPA to DHA and GLA has been used with clinical efficacy – improving fatty acid blood composition [40], ADHD scores [25] and reading ability in mainstream children [6]. As erythrocytes typically only survive in the body for around 120 days supplementation trials shorter than this may not be long enough to detect changes in fatty acids concentrations and compositions [9,50]. Furthermore, the turnover of fatty acids in the brain is thought to be rather low in 6 to 12 years old, indicating that longer periods of supplementation and/or higher doses may be needed to modify the fatty acid content of their central nervous system [65]. Future studies should also account for possible interaction effects of age, apoliprotein E genotype, gender and include brain imaging techniques to further study underpinning mechanisms [9]. In some studies, the absence of a measure of baseline fatty acid status, such as percentage of DHA in erythrocytes or monitoring of subsequent changes is another design weakness that can make the generality of some findings uncertain [57]. It is also possible that certain outcome measures such as the Connors Teaching Rating Scale are not sensitive enough to detect small improvements in behaviour [66]. Teacher rating scales have been regarded as being problematic and multiple questions have been raised regarding their reliability [66].

With regard to general limitations more RCTs are needed for other learning-related conditions and problems such as ASD, dyslexia and Developmental Co-ordination Disorder (also known as Dyspraxia) alongside continued research into the significance of maternal omega-3/6 fatty acid consumption. Whilst some studies indicate general dietary inadequacies [67] and selective eating habits [68] amongst such groups, detailed trials are needed. There is also some evidence that brain inflammation may be involved in the pathogenesis of neuropsychiatric diseases such as autism [52] which could impact on omega-3 requirements**.** The effects of nutrient combinations (zinc, magnesium, iron) alongside omega fatty acids also warrants further study as this may provide greater benefits than isolated nutrients [69]. More focused research is also needed on under-represented groups such as looked after children who are more likely to be omega deplete.

Conclusions

In conclusion, a growing body of evidence indicates that supplementing the diet with omega-3/6 fatty acids may help to reduce ADHD symptoms in children and young people and could assist mainstream school populations. Latest clinical evidence points towards improvements in reading, spelling, attention and behaviour, in particular. Strongest evidence exists for those with: 1) ADHD or comorbid conditions. 2) Suboptimal omega-3 status or 3) Academic underperformers. It is now important to communicate such findings to early year's providers, parents, carers, schools and those who are in contact with children and young people that could benefit from omega 3/6 fatty acids during their years of learning.

Conflict of Interest

This review was supported by Equazen. The views expressed are those of the authors alone and Equazen had no role in writing the review.

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References

1. Gow RV, Hibbeln JR (2014) Omega-3 fatty acid and nutrient deficits in adverse neurodevelopment and childhood behaviors. Child Adolesc Psychiatr Clin N Am 23: 555-590.
2. Simopoulos AP (2011) Evolutionary aspects of diet: the omega-6/omega-3 ratio and the brain. Mol Neurobiol 44: 203-215.
3. Chang CY, Ke DS, Chen JY (2009) Essential fatty acids and human brain. Acta Neurol Taiwan 18: 231-241.
4. Su HM (2010) Mechanisms of n-3 fatty acid-mediated development and maintenance of learning memory performance. J Nutr Biochem 21: 364-373.
5. Gharami K, Das M, Das S (2015) Essential role of docosahexaenoic acid towards development of a smarter brain. Neurochem Int 89: 51-62.
6. Johnson M, Fransson G, Ostlund S, Areskoug B, Gillberg C (2017) Omega 3/6 fatty acids for reading in children: a randomized, double-blind, placebo-controlled trial in 9-year-old mainstream schoolchildren in Sweden. J Child Psychol Psychiatry 58: 83-93.
7. Raz R, Gabis L (2009) Essential fatty acids and attention-deficit-hyperactivity disorder: a systematic review. Dev Med Child Neurol 51: 580-592.
8. Innis SM (2007) Dietary (n-3) fatty acids and brain development. J Nutr 137: 855-859.
9. Stonehouse W (2014) Does consumption of LC omega-3 PUFA enhance cognitive performance in healthy school-aged children and throughout adulthood? Evidence from clinical trials. Nutrients 6: 2730-2758.
10. Rise P, Tragni E, Ghezzi S, Agostoni C, Marangoni F, et al. (2013) Different patterns characterize Omega 6 and Omega 3 long chain polyunsaturated fatty acid levels in blood from Italian infants, children, adults and elderly. Prostaglandins Leukot Essent Fatty Acids 89: 215-220.
11. Montgomery P, Burton JR, Sewell RP, Spreckelsen TF, Richardson AJ (2013) Low blood long chain omega-3 fatty acids in UK children are associated with poor cognitive performance and behavior: a cross-sectional analysis from the DOLAB study. PLoS One 8: e66697.
12. Tammam JD, Steinsaltz D, Bester DW, Semb-Andenaes T, Stein JF (2016) A randomised double-blind placebo-controlled trial investigating the behavioural effects of vitamin, mineral and n-3 fatty acid supplementation in typically developing adolescent schoolchildren. Br J Nutr 115: 361-373.
13. Stevens LJ, Zentall SS, Abate ML, Kuczek T, Burgess JR (1996) Omega-3 fatty acids in boys with behavior, learning, and health problems. Physiol Behav 59: 915-920.
14. Missaoui S, Gaddour N, Gaha L (2014) Prevalence of specific learning disorders in a cohort of children with school failure. Tunis Med 92: 570-573.
15. Zelcer M, Goldman RD (2015) Omega-3 and dyslexia: uncertain connection. Can Fam Physician 61: 768-770.
16. Hawkey E, Nigg JT (2014) Omega-3 fatty acid and ADHD: blood level analysis and meta-analytic extension of supplementation trials. Clin Psychol Rev 34: 496-505.
17. Cooper RE, Tye C, Kuntsi J, Vassos E, Asherson P (2016) The effect of omega-3

polyunsaturated fatty acid supplementation on emotional dysregulation, oppositional behaviour and conduct problems in ADHD: A systematic review and meta-analysis. J Affect Disord 190: 474-482.

18. Parletta N, Niyonsenga T, Duff J (2016) Omega-3 and Omega-6 polyunsaturated fatty acid levels and correlations with symptoms in children with attention deficit hyperactivity disorder, autistic spectrum disorder and typically developing controls. PLoS One 11: e0156432.
19. Tooley UA, Makhoul Z, Fisher PA (2016) Nutritional status of foster children in the U.S.: implications for cognitive and behavioral development. Child Youth Serv Rev 70: 369-374.
20. Huffman SL, Harika RK, Eilander A, Osendarp SJ (2011) Essential fats: how do they affect growth and development of infants and young children in developing countries? A literature review. Matern Child Nutr 7: 44-65.
21. Innis SM (2008) Dietary omega 3 fatty acids and the developing brain. Brain Res 1237: 35-43.
22. Mueller A, Hong DS, Shepard S, Moore T (2017) Linking ADHD to the neural circuitry of attention. Trends Cogn Sci 21: 474-488.
23. Gow RV, Hibbeln JR, Parletta N (2015) Current evidence and future directions for research with omega-3 fatty acids and attention deficit hyperactivity disorder. Curr Opin Clin Nutr Metab Care 18: 133-138.
24. Groenman AP, Schweren LJ, Dietrich A, Hoekstra PJ (2017) An update on the safety of psychostimulants for the treatment of attention-deficit/hyperactivity disorder. Expert Opin Drug Saf 16: 455-464.
25. Barragan E, Breuer D, Dopfner M (2017) Efficacy and safety of Omega-3/6 fatty acids, methylphenidate, and a combined treatment in children with ADHD. J Atten Disord 21:433-441.
26. Swanson JM, Arnold LE, Molina BSG, Sibley MH, Hechtman LT, et al. (2017) Young adult outcomes in the follow-up of the multimodal treatment study of attention-deficit/hyperactivity disorder: symptom persistence, source discrepancy, and height suppression. J Child Psychol Psychiatry 58: 663-678.
27. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A (2016) Rayyan — a web and mobile app for systematic reviews. Syst Rev 5: 210.
28. Liu JC, Raine A, Ang RP, Fung DS (2015) An analysis of blinding success in a randomised controlled trial of fish oil omega-3 fatty acids. Ann Acad Med Singapore 44: 85-91.
29. Milte CM, Parletta N, Buckley JD, Coates AM, Young RM, et al. (2015) Increased erythrocyte eicosapentaenoic acid and docosahexaenoic acid are associated with improved attention and behavior in children with ADHD in a randomized controlled three-way crossover trial. J Atten Disord 19: 954-964.
30. Milte CM, Parletta N, Buckley JD, Coates AM, Young RM, et al. (2012) Eicosapentaenoic and docosahexaenoic acids, cognition, and behavior in children with attention-deficit/hyperactivity disorder: a randomized controlled trial. Nutrition 28: 670-677.
31. Anand P, Sachdeva A (2016) Effect of poly unsaturated fatty acids administration on children with attention deficit hyperactivity disorder: a randomized controlled trial. J Clin Diagn Res 10: OC01-OC05.
32. Bos DJ, Oranje B, Veerhoek ES, Van Diepen RM, Weusten JM, et al. (2015) Reduced symptoms of inattention after dietary Omega-3 fatty acid supplementation in boys with and without attention deficit/hyperactivity disorder. Neuropsychopharmacology 40: 2298-2306.
33. Wu Q, Zhou T, Ma L, Yuan D, Peng Y (2015) Protective effects of dietary supplementation with natural omega-3 polyunsaturated fatty acids on the visual acuity of school-age children with lower IQ or attention-deficit hyperactivity disorder. Nutrition 31: 935-940.
34. Widenhorn-Muller K, Schwanda S, Scholz E, Spitzer M, Bode H (2014) Effect of supplementation with long-chain omega-3 polyunsaturated fatty acids on behavior and cognition in children with attention deficit/hyperactivity disorder (ADHD): a randomized placebo-controlled intervention trial. Prostaglandins Leukot Essent Fatty Acids 91: 49-60.
35. Manor I, Magen A, Keidar D, Rosen S, Tasker H, et al. (2013) Safety of phosphatidylserine containing omega3 fatty acids in ADHD children: a double-blind placebo-controlled trial followed by an open-label extension. Eur Psychiatry 28: 386-391.
36. Hariri M, Djazayery A, Djalali M, Saedisomeolia A, Rahimi A, et al. (2012) Effect of n-3 supplementation on hyperactivity, oxidative stress and inflammatory mediators in children with attention-deficit-hyperactivity disorder. Malays J Nutr 18: 329-335.
37. Bent S, Hendren RL, Zandi T, Law K, Choi JE, et al. (2014) Internet-based, randomized, controlled trial of omega-3 fatty acids for hyperactivity in autism. J Am Acad Child Adolesc Psychiatry 53: 658-666.
38. Gabbay V, Babb JS, Klein RG, Panzer AM, Katz Y, et al. (2012) A double-blind, placebo-controlled trial of omega-3 fatty acids in Tourette's disorder. Pediatrics 129: e1493-1500.
39. Portillo-Reyes V, Perez-Garcia M, Loya-Mendez Y, Puente AE (2014) Clinical significance of neuropsychological improvement after supplementation with omega-3 in 8-12 years old malnourished Mexican children: a randomized, double-blind, placebo and treatment clinical trial. Res Dev Disabil 35: 861-870.
40. Johnson M, Mansson JE, Ostlund S, Fransson G, Areskoug B, et al. (2012) Fatty acids in ADHD: plasma profiles in a placebo-controlled study of Omega 3/6 fatty acids in children and adolescents. Atten Defic Hyperact Disord 4: 199-204.
41. Manor I, Magen A, Keidar D, Rosen S, Tasker H, et al. (2012) The effect of phosphatidylserine containing Omega3 fatty-acids on attention-deficit hyperactivity disorder symptoms in children: a double-blind placebo-controlled trial, followed by an open-label extension. Eur Psychiatry 27: 335-342.
42. Perera H, Jeewandara KC, Seneviratne S, Guruge C (2012) Combined omega3 and omega6 supplementation in children with attention-deficit hyperactivity disorder (ADHD) refractory to methylphenidate treatment: a double-blind, placebo-controlled study. J Child Neurol 27: 747-753.
43. Kirby A, Woodward A, Jackson S, Wang Y, Crawford MA (2010) A double-blind, placebo-controlled study investigating the effects of omega-3 supplementation in children aged 8-10 years from a mainstream school population. Res Dev Disabil 31: 718-730.
44. Raine A, Portnoy J, Liu J, Mahoomed T, Hibbeln JR (2015) Reduction in behavior problems with omega-3 supplementation in children aged 8-16 years: a randomized, double-blind, placebo-controlled, stratified, parallel-group trial. J Child Psychol Psychiatry 56: 509-520.
45. Richardson AJ, Burton JR, Sewell RP, Spreckelsen TF, Montgomery P (2012) Docosahexaenoic acid for reading, cognition and behavior in children aged 7-9 years: a randomized, controlled trial (the DOLAB Study). PLoS One 7: e43909.
46. Arnold L, Young A, Belury M, Cole RM, Gracious B, et al. (2017) Omega-3 fatty acid plasma levels before and after supplementation: correlations with mood and clinical outcomes in the omega-3 and therapy studies. J Child Adolesc Psychopharmacol 27: 223-233.
47. Montgomery P, Burton JR, Sewell RP, Spreckelsen TF, Richardson AJ (2014) Fatty acids and sleep in UK children: subjective and pilot objective sleep results from the DOLAB study--a randomized controlled trial. J Sleep Res 23: 364-388.
48. Christian LM, Young AS, Mitchell AM, Belury MA, Gracious BL, et al. (2017) Body weight affects omega-3 polyunsaturated fatty acid (PUFA) accumulation in youth following supplementation in post-hoc analyses of a randomized controlled trial. PLoS One 12: e0173087.
49. Fourneret P, Poissant H (2016) [Learning disorders in ADHD: how are they related?]. Arch Pediatr 23: 1276-1283.
50. Matsudaira T, Gow RV, Kelly J, Murphy C, Potts L, et al. (2015) Biochemical and psychological effects of omega-3/6 supplements in male adolescents with attention-deficit/hyperactivity disorder: a randomized, placebo-controlled, clinical trial. J Child Adolesc Psychopharmacol 25: 775-782.
51. Assareh M, Davari Ashtiani R, Khademi M, Jazayeri S, Rai A, et al. (2017) Efficacy of polyunsaturated fatty acids (pufa) in the treatment of attention deficit hyperactivity disorder. J Atten Disord 21: 78-85.
52. Theoharides TC, Asadi S, Patel AB (2013) Focal brain inflammation and autism. J Neuroinflammation 10: 46.
53. Voigt RG, Mellon MW, Katusic SK, Weaver AL, Matern D, et al. (2014) Dietary docosahexaenoic acid supplementation in children with autism. J Pediatr Gastroenterol Nutr 58: 715-722.
54. Du JC, Chiu TF, Lee KM, Wu HL, Yang YC, et al. (2010) Tourette syndrome in children: an updated review. Pediatr Neonatol 51: 255-264.
55. Kuratko CN, Barrett EC, Nelson EB, Salem N Jr (2013) The relationship of docosahexaenoic acid (DHA) with learning and behavior in healthy children: a review. Nutrients 5: 2777-2810.
56. Bauer I, Hughes M, Rowsell R, Cockerell R, Pipingas A, et al. (2014) Omega-3 supplementation improves cognition and modifies brain activation in young adults. Hum Psychopharmacol 29: 133-144.

57. Benton D, Donohoe RT, Clayton DE, Long SJ (2013) Supplementation with DHA and the psychological functioning of young adults. Br J Nutr 109: 155-161.

58. Baumgartner J, Smuts CM, Malan L, Kvalsvig J, van Stuijvenberg ME, et al. (2012) Effects of iron and n-3 fatty acid supplementation, alone and in combination, on cognition in school children: a randomized, double-blind, placebo-controlled intervention in South Africa. Am J Clin Nutr 96: 1327-1338.

59. Baym CL, Khan NA, Monti JM, Raine LB, Drollette ES, et al. (2014) Dietary lipids are differentially associated with hippocampal-dependent relational memory in prepubescent children. Am J Clin Nutr 99: 1026-1032.

60. Bates Bea (2016) National Diet and Nutrition Survey: results from years 5 and 6 (combined) of the Rolling Programme (2012/2013 - 2013/2014). TSO: London.

61. Konigs A, Kiliaan AJ (2016) Critical appraisal of omega-3 fatty acids in attention-deficit/hyperactivity disorder treatment. Neuropsychiatr Dis Treat 12: 1869-1882.

62. Chang JC, Su KP, Mondelli V, Pariante CM (2017) Omega-3 polyunsaturated fatty acids in youths with attention deficit hyperactivity disorder (adhd): a systematic review and meta-analysis of clinical trials and biological studies. Neuropsychopharmacology 43: 534-545.

63. Bos DJ, van Montfort SJ, Oranje B, Durston S, Smeets PA (2016) Effects of omega-3 polyunsaturated fatty acids on human brain morphology and function: what is the evidence? Eur Neuropsychopharmacol 26: 546-561.

64. Berger ME, Smesny S, Kim SW, Davey CG, Rice S, et al. (2017) Omega-6 to omega-3 polyunsaturated fatty acid ratio and subsequent mood disorders in young people with at-risk mental states: a 7-year longitudinal study. Transl Psychiatry 7: e1220.

65. Voigt RG, Llorente AM, Jensen CL, Fraley JK, Berretta MC, et al. (2001) A randomized, double-blind, placebo-controlled trial of docosahexaenoic acid supplementation in children with attention-deficit/hyperactivity disorder. J Pediatr 139: 189-196.

66. Sinn N, Bryan J (2007) Effect of supplementation with polyunsaturated fatty acids and micronutrients on learning and behavior problems associated with child ADHD. J Dev Behav Pediatr 28: 82-91.

67. Mari-Bauset S, Llopis-Gonzalez A, Zazpe-Garcia I, Mari-Sanchis A, Morales-Suarez-Varela M (2015) Nutritional status of children with autism spectrum disorders (ASDs): a case-control study. J Autism Dev Disord 45: 203-212.

68. Zimmer MH, Hart LC, Manning-Courtney P, Murray DS, Bing NM, et al. (2012) Food variety as a predictor of nutritional status among children with autism. J Autism Dev Disord 42: 549-556.

69. Lange KW, Hauser J, Lange KM, Makulska-Gertruda E, Nakamura Y, et al. (2017) The role of nutritional supplements in the treatment of ADHD: what the evidence says. Curr Psychiatry Rep 19: 8.