Universiteit
Leiden
The Netherlands

Dietary supplements for aggressive behavior: studies in people with intellectual disability

Gast, D.A.A.

Citation
Gast, D. A. A. (2022, November 29). *Dietary supplements for aggressive behavior: studies in people with intellectual disability*. Retrieved from https://hdl.handle.net/1887/3492068

Version:	Publisher's Version
License:	Licence agreement concerning inclusion of doctoral thesis in the Institutional Repository of the University of Leiden
Downloaded from:	https://hdl.handle.net/1887/3492068

Note: To cite this publication please use the final published version (if applicable).

Chapter 6

EFFECTIVENESS OF MULTIVITAMIN AND MINERAL SUPPLEMENTATION ON AGGRESSIVE BEHAVIOR: A SYSTEMATIC REVIEW AND META-ANALYSIS

Submitted for publication as:

D.A.A. Gast, T.A. Wissink, A.M. van Hemert, R. Didden, E.J. Giltay; Effectiveness of Multivitamin and Mineral Supplementation on Aggressive Behavior: A Systematic Review and Meta-Analysis

ABSTRACT

Background: Randomized controlled trials (RCTs) reported beneficial effects of multivitamin and mineral supplements on aggressive behavior. However, the strength of the association differed across populations, and it is unknown whether the effects on observed incidents or more subjective (continuous) outcome measures are consistent. We aimed to investigate the overall effectiveness of multivitamin and mineral supplements on aggressive behavior in a systematic review with meta-analysis.

Methods: Systematic searches were performed in the databases Cochrane Library, Embase, PsycINFO, and PubMed for all RCTs that used multivitamins/minerals (with or without n-3 PUFA) versus a control group with at least one measure of aggressive behavior. Two meta-analyses were conducted using a random-effects model, one with the pooled Hedges' *g* effect sizes for continuous outcome data and one with the incidence rate ratios for count outcome data (IRR).

Results: Eleven RCTs met the inclusion criteria, yielding 18 effect sizes. There were 948 subjects in the multivitamins/mineral group and 811 in the control group. The supplements showed substantial variation in micronutrient doses and composition across trials. The target groups of the studies consisted of young adult prisoners, school-aged youth and students, psychiatric patients, and people with an intellectual disability. Multivitamin/mineral intervention versus placebo reduced aggressive behavior, with an IRR of 0.72, 95% confidence interval (CI) [0.56, 0.93], for the count data, and a Hedges' *g* of -0.23, 95% CI [-0.38, -0.07], for the continuous data.

Conclusion: Multivitamin mineral supplements versus placebo showed a small but significant pooled beneficial effect size on aggressive behavior.

INTRODUCTION

Aggressive behavior is a serious problem among various institutional groups, such as psychiatric patients, adolescent prisoners, and people with intellectual disabilities (Bader, Evans, & Welsh, 2014; Bowring, Painter, & Hastings, 2019; Emerson et al., 2001; Steiner & Cain, 2016). For victims it can be harmful or traumatizing (Needham, Abderhalden, Halfens, Fischer, & Dassen, 2005), and for the aggressor it is associated with institutionalization and medicalization (Didden et al., 2016). Aggressive behavior may also cause chronic stress, increased workload, and burnout for professionals who care for aggressive clients or patients (Hensel, Lunsky, & Dewa, 2012). There is a range of interventions to prevent aggressive behavior (Lee & DiGiuseppe, 2018; Lloyd & Kennedy, 2014), but they all have their inherent limitations and side effects. Vitamin/mineral supplementation may provide a cost-effective, accessible, and well-tolerated adjunct to the standard treatments for aggressive behavior.

Positive effects of micronutrients on behavior have been found in an open-label trial (Hambly et al., 2017) and in several randomized controlled trials (RCTs; (Gesch, Hammond, Hampson, Eves, & Crowder, 2002; Rucklidge, Eggleston, Johnstone, Darling, & Frampton, 2018; Schoenthaler et al., 1997; Zaalberg, Nijman, Bulten, Stroosma, & Van Der Staak, 2010). There are several hypotheses about underlying mechanisms. Micronutrients are involved in the synthesis of neurotransmitters (Calderon-Ospina & Nava-Mesa, 2020), and B-vitamins and minerals play an important role in the energy production of the central nervous system (Kennedy, 2016). Also, micronutrients contribute to healthy functioning and longevity of neurons and their connectivity (Parletta, Milte, & Meyer, 2013). Furthermore, micronutrients may help to maintain a healthy microbiome, which may affect behavior through the gut–brain axis (Choi et al., 2020; Liu et al., 2017; Luthold, Fernandes, Franco-de-Moraes, Folchetti, & Ferreira, 2017). Over all, the effect of vitamins and minerals is best understood as a complex interplay between multiple micronutrients, which is also found in a healthy and balanced diet, and less as the effect of a single micronutrient on a single process (Messina, Lampe, Birt, & Appel, 2001; Parletta et al., 2013).

Several systematic reviews on the effect of dietary supplements on behavior have been published so far. However, many reviews focused on omega-3 fatty acids (FAs) rather than multivitamins and minerals (Bent, Bertoglio, & Hendren, 2009; Bozzatello, Brignolo, De Grandi,

& Bellino, 2016; Choy & Raine, 2018; Cooper, Tye, Kuntsi, Vassos, & Asherson, 2016; Gajos & Beaver, 2016; Gould, Roberts, & Makrides, 2021). Two systematic reviews performed a meta-analysis of RCTs on the effect of only omega-3 FA supplementation on aggression, with pooled effect sizes ranging from small to medium (Cooper et al., 2016; Gajos & Beaver, 2016). Five systematic reviews were published on the effect of multivitamin and mineral supplements on behavioral outcomes. The outcome measures of the reviews differed between trials and included behavior and cognition in general (Frensham, Bryan, & Parletta, 2012), behavior within psychiatric disorders (Johnstone, Hughes, Goldenberg, Romijn, & Rucklidge, 2020; Rucklidge & Kaplan, 2013), and anti-social and criminal behavior (Benton, 2007). Another review had aggressive behavior as outcome, but did not distinguish between single micronutrient interventions and multivitamin and mineral supplements (Qureshi, Kunaratnam, Kolla, & Konkoly Thege, 2021).

To the best of our knowledge, no meta-analysis on the effect of multivitamin and mineral supplements on aggressive behavior has been conducted to date. Therefore, the aim of this meta-analysis was to investigate whether multivitamin and mineral supplementation is effective and safe in reducing aggressive behavior and to explore potential sources of heterogeneity.

METHODS

Search strategy

We searched through the following databases: Cochrane Library, Embase, PubMed, and PsycINFO. We took into account all literature up to December 12, 2020. In addition, we checked all reference lists of the main articles and contacted the expert authors. The Boolean search string consisted of three parts: aggressive behaviors, AND dietary supplements, AND RCT (Appendix 1). Furthermore, in the reference list of the relevant articles, we searched for additional literature, and finally we contacted five experts and asked them to provide additional data. We exported the results of the search strategy to EndNote (Clarivate, 2019).

Eligibility criteria and study selection

In our meta-analysis, we included randomized placebo controlled trials (RCT) that used oral multivitamin/mineral supplements as an intervention alongside diet as usual and aggressive

behavior as an outcome. No selection was made regarding the setting of the study or the age and background of the participants. The dietary supplement had to contain a combination of at least five vitamins and four minerals but could also contain other micronutrients. We used a broad inclusive definition of aggressive behavior: harmful behavior that violates social norms (Bandura, 1973). All trials with at least one outcome meeting that definition were included in our meta-analysis. To operationalize aggression, we used the counts of incidents as well as measures like self-report and observer-rated questionnaires. This included measurements of conduct problems, rule offending behavior, anti-social behavior, disruptive behavior, and other externalizing behaviors.

After removing duplicates, we selected articles via titles. The next selection we made via abstracts, after which we assessed the full-text article.

Data extraction

The following data were extracted: study design, sample size, timeline, intervention details, outcome measures, and overall results. We also extracted characteristics of the participants, including age, gender, setting, medical diagnosis, and psychotropic medication. The internal validity of the trials was assessed using the Cochrane Risk of Bias Tool that features seven criteria: random sequence generation, allocation concealment, participant blinding, outcome data blinding, incomplete outcome data, selective reporting, and other biases (Higgins et al., 2011).

Two separate pooled effect sizes were calculated: an incidents rate ratio (IRR) for the count-data outcome and a Hedges' *g* for the continuous data (Hedges, 1986). The interpretation of an IRR can be compared to that of an odds ratio, whereby a value of 1 represents no effect. The magnitude of Hedges' *g* can be interpreted as small (0.20), moderate (0.50), or large (0.80; (Fritz, Morris, & Richler, 2012).

To be able to import them into the Comprehensive Meta-Analysis (CMA), we (re)calculated the IRR of four trials (Gesch et al., 2002; Schoenthaler et al., 1997; Schoenthaler & Bier, 2000; Tammam, Steinsaltz, Bester, Semb-Andenaes, & Stein, 2016) using the OpenEpi calculator (Sullivan, Dean, & Soe, 2009). From the study of Gesch et al. (2002), we extracted additional information on the data from Gesch's PhD thesis (Gesch, 2011). From Tamman et al. (2016), additional information was gleaned from the supplementary material (S1). Finally, we corresponded directly with Schoenthaler et al. (1997, 2000 & 2021) to gain further information for our dataset. To avoid selection bias, we made a correction for one study outcome of

Schoenthaler et al. (2000). This study excluded 308 of 388 participants who had no incidents during the intervention. We reanalyzed the effect size by including these 308 participants in the analysis. In a three-arm study (Schoenthaler, Gast, Giltay, & Amos, 2021), the two active arms were combined to avoid a unit-of-analysis error (Rucker, Cates, & Schwarzer, 2017). Random and fixed effects were calculated and the difference between these outcomes was assessed as an indication for risk of heterogeneity (Higgins & Green, 2011). We further investigated the risk of heterogeneity using the Q value, the I-squared (I^2), and Tau-squared (T^2) statistics. A difference between the Q value and the df(Q) indicates heterogeneity. Furthermore I^2 indicates which proportion of the variance can be attributed to a difference in effect sizes and not to the SE. Publication bias was assessed using the Egger test and by visual examination of the funnel plot (Jin, Zhou, & He, 2015). All steps including the search, selection, extraction, and analysis were performed independently by two researchers (first and second authors). Inconsistencies regarding the results were discussed with a third researcher (last author) until consensus was reached. The data were analyzed using CMA (Clarivate, 2019).

RESULTS

Study selection

As depicted in the flow chart (Figure 6.1), the search strategy identified 1003 records, from which we removed 164 duplicates. We screened the remaining 839 articles, yielding 11 trials that we included in the meta-analysis.

Study characteristics

The study characteristics are summarized in Table 6.1. The trials were published between 1997 and 2018; two trials were still under submission (De Bles et al., 2022; Gast et al., 2022).The number of participants per study ranged from 71 to 468, for a total of 2466. We included 1759 participants (71.3%) in our analyses, whereof 948 (53.9%) received the active supplements. Seven of the 11 trials included women; the total number of women in the statistical analysis was 285 (16.2%). Participants included people with psychiatric symptoms and people with intellectual disabilities (Adams et al., 2011; De Bles et al., 2022; Gast et al., 2022; Rucklidge et al., 2018) prisoners (Gesch et al., 2002; Schoenthaler et al., 1997; Schoenthaler et al., 2021; Zaalberg et al., 2010), and school-aged children and university students (Long & Benton, 2013;

Schoenthaler & Bier, 2000; Tammam et al., 2016). In five out of 11 trials, the intervention with vitamins and minerals was supplemented with omega-3 FAs (De Bles et al., 2022; Gast et al., 2022; Gesch et al., 2002; Tammam et al., 2016; Zaalberg et al., 2010). The intervention periods ranged from 2 weeks to 9 months.

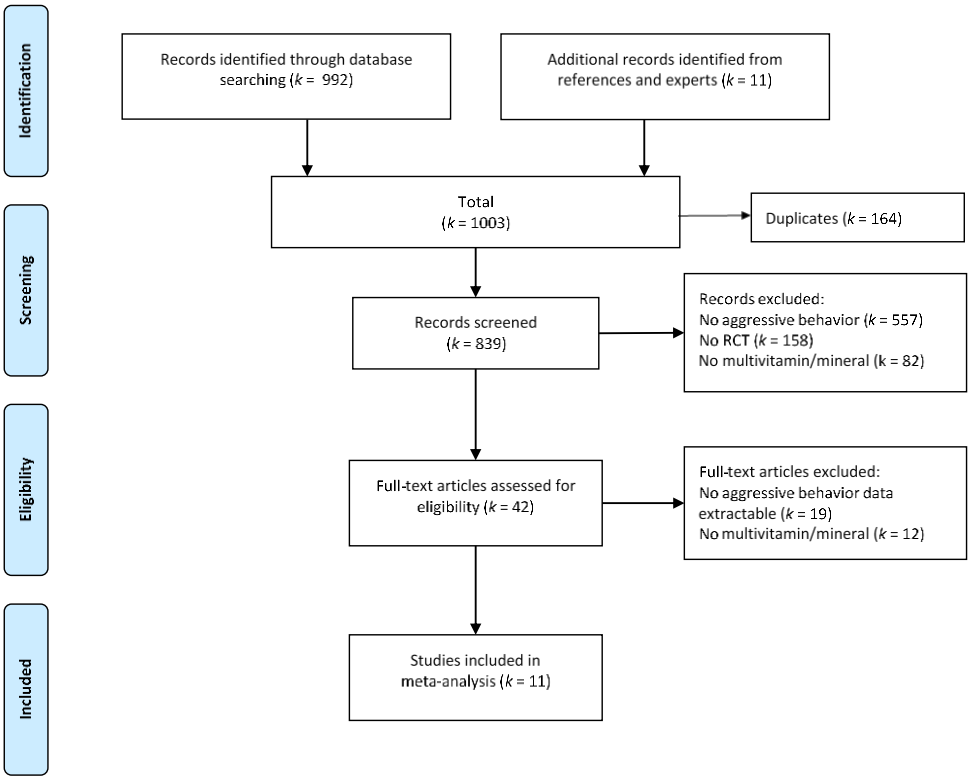

Figure 6.1 Flow chart

Measurements

Various methods have been used to measure aggressive behaviors, which we categorized into two groups: (a) the count of observed aggression-related incidents and (b) the use of data from continuous scales. Three trials used incident counts as a single outcome (Schoenthaler et al., 1997; Schoenthaler & Bier, 2000; Schoenthaler et al., 2021). Three trials used continuous scales as a single outcome (Adams et al., 2011; Long & Benton, 2013; Rucklidge et al., 2018), and five trials used both (De Bles et al., 2022; Gast et al., 2022; Gesch et al., 2002; Tammam et al., 2016; Zaalberg et al., 2010). In the prison and school trials, we used the institutional reported rule violations (Gesch, 2011; Schoenthaler et al., 1997; Schoenthaler et al., 2021; Zaalberg et al., 2010) to count the incidents. De Bles et al. (2022) used the Staff Observation

Aggression Scale-Revised (Nijman et al., 1999), and Gast et al. (2022) used the Modified Overt Aggression Scale (Oliver, Crawford, Rao, Reece, & Tyrer, 2007).

Table 6.1 provides an overview of the measuring instruments used in the various studies. For the continuous data, 8 questionnaires or scales were used to measure aggressive behaviors. Of these, four were self-report scales; namely, three different versions of the Aggression Questionnaire (Bryant & Smith, 2001; Buss & Perry, 1992) were used (De Bles et al., 2022; Long & Benton, 2013; Zaalberg et al., 2010) and Gesch et al. (2002) used the Survey Anger Scales (O'Rourke, 1994). Furthermore, five proxy reported scales were used. The Social Dysfunction and Aggression Scale (SDAS; (Wistedt et al., 1990) was used in three trials (De Bles et al., 2022; Gast et al., 2022; Zaalberg et al., 2010). Different versions of the Conners Behaviors Scales (Conners, Sitarenios, Parker, & Epstein, 1998) were used in two trials (Rucklidge et al., 2018; Tammam et al., 2016). Furthermore, Rucklidge et al. (2018) used the Parent/Teacher Strengths and Difficulties Questionnaires (SDQ; (Goodman, 2001), and Adams et al. (2011) used the Parent Global Impressions-Revised (PGI-r; Adams & Holloway, 2004).

Main effect

From eleven trials, we extracted 18 effect sizes that were included in our meta-analysis—eight trials and eight effect sizes came from count data, and seven trials and 10 effect sizes from continuous data. This yielded two pooled random effect sizes. We found an IRR of 0.72, 95% confidence interval (CI) [0.56, 0.93], p = .011, for the count data and a Hedges' g of -0.23, 95% CI [-0.38, -0.07], p = .001, for the continuous data (Figure 6.2 and 6.3).

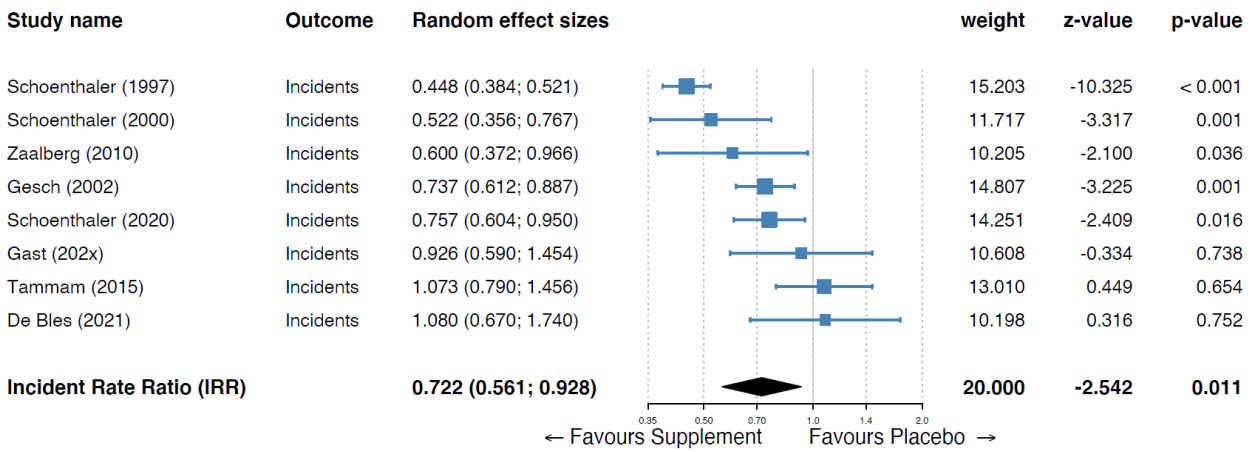

Figure 6.2. Effect sizes (rate ratio) of the externalizing behavior incidents counts.

Table 6.1. Characteristics of included studies (*k* = 11)

Study	*N* (analyzed)	Fem. %	Age (years)	population	Intervention (*n*)	Duration	Outcome measures aggressive behavior	Results
Adams et al. (2011)	141 (104)	11.3%	3–60, *M* = 10.8	Children and adults with ASD	(13)Vi & (13)Mi (*n*=**53**) vs. Pla (*n*=**5**1)	3 m	CS: Parental Global Impressions Revised, subscale tantrumming	Decrease of tantrumming score in active vs. placebo group; *d* = .51, *p* = .009. More withdrawals due to adverse effects in placebo group
De Bles et al. (2022)	176 (176)	35.8%	*M* = 49.3 (14.5)	Psychiatric patients	(12)Vi & (8)Mi & (2)EFA (*n*=87) vs. Pla (*n*=89)	6 m	CD: Incidents reported with the staff observation aggression scale–revised (SOAS-r) CS: Social Dysfunction and Aggression Scale (SDAS-11) and AVL-AV	No significant difference on any outcome measure. More burping in active group (adverse event)
Gast et al. (2022)	113 (113)	34.5%	*M* = 22.8 (7.2)	People with intellectual disabilities	(12)Vi & (9)Mi & (2)EFA (*n*=57) vs. Pla (*n*=56)	16 w	CD: Incidents reported with Modified Overt Aggression Scale (MOAS) CS: SDAS-11	No significant difference on any outcome measure, nor on reported adverse events
Gesch et al. (2002)	231 (231)	0%	18–21	Young adult prisoners	(12)Vi & (12)Mi & (4)EFA (*n*=116) vs. Pla (*n*=115)	2 w–9 m	CD: Number of reported prison rule offences	Decrease of offences in active vs. placebo group 26.3% (95% CI [8.3, 44.3%]); *p* = .03. No adverse effects have been reported.
Long et al. (2013)	202 (85)	0%	*M* = 20.9	Young adult men	(13)Vi & (13)Mi & (2)EFA (*n*=43) vs. Placebo (*n*=42)	3 m	CS: Aggression Questionnaire (AQ)	No significant difference in score on AQ active vs. placebo; *d* = −.24, *p* > .05, nor on the reported side effects
Rucklidge et al. (2018)	93 (93)	23.7%	7–12	Children with ADHD	(13)Vi & (17)Mi (*n*=47) vs. Placebo (*n*=46)	10 w	CS: Parental strengths and difficulties questionnaire (SDQ): conduct problems score; Teacher SDQ: conduct problems score	Decrease of parent SDQ score in active group: *d* = 0.52, *p* = .015. No significant difference on teacher SDQ score in active group *d* = 0.47, *p* = .055, nor on reported adverse events
Schoenthaler et al. (1997)	71 (62)	33.9%	13–17	Adolescent prisoners	(12)Vi & (11)Mi (*n*=32) vs. Pla (*n*=30)	3 m	CD: Number of reported prison rule offences	Decrease of offences in active vs. placebo group; RR = .45, (95% CI [.38, .52]). No adverse events have been reported
Schoenthaler et al. (2000)	468 (80)	31.3%	6–12	Children	(13)Vi & (10)Mi (*n*=40) vs. Placebo (*n*=40)	4 m	CD: Number of reported school offences	Decrease of offences in active vs. placebo group; RR = .52, (95% CI [.36, .77]). No adverse events have been reported.
Schoenthaler et al. (2021)	449 (398)	0%	18–24	Young adult prisoners	(13)Vi & (6–10)Mi (*n*=260) vs. Pla (*n*=138)	15 w	CD: Number of reported prison rule offences	Decrease of offences in active group; RR = .76 (95% CI [.61, .95]). No adverse events have been reported.
Tammam et al. (2016)	196 (196)	50%	13–16	Adolescents	(12)Vi & (8)Mi & (2)EFA (*n*=98) vs. Pla (*n*=98)	12 w	CD: number of school rule offences CS: Conners teacher rating assessment Subscale: Disruptive behavior	No significant difference number of offences in active vs. placebo group; *d* = .039, *SE* =.154. Decrease of disruptive behavior in active group vs. placebo group; *d* = 0.35, *p* = .02. No reported adverse events
Zaalberg et al. (2010)	326 (221)	(0%)	18–25	Young adult prisoners	(12)Vi & (12)Mi & (3)EFA (*n*=115) vs. Pla (*n*=106)	1–3 m	CD: Number of reported prison rule offences. CS: SDAS; Aggression Questionnaire (AQ)	SDAS: no significant difference, *p* = .23 (one-tailed); AQ: no significant difference, *p* = .091; Incident rate 40% decrease (95% CI [4, 63]) (one-tailed) intervention vs. placebo. No reported adverse events

ADHD = attention deficit/hyperactivity disorder; **ASD** = autism spectrum disorder; **AVL-AV** = a Dutch aggression questionnaire; **CBT** = cognitive behavioral therapy; **CD** = count data; **CS** = continuous scale; ***d*** = Cohen's *d*; (X)**EFA** = (number of) essential fatty acids; ***k*** = number of studies; **m** = months; *M* = mean; (X)**Mi** = (number of) minerals; **NS** = No supplements; **Pla** = Placebo; (X)**Vi**= (number of) vitamins; **w** = weeks

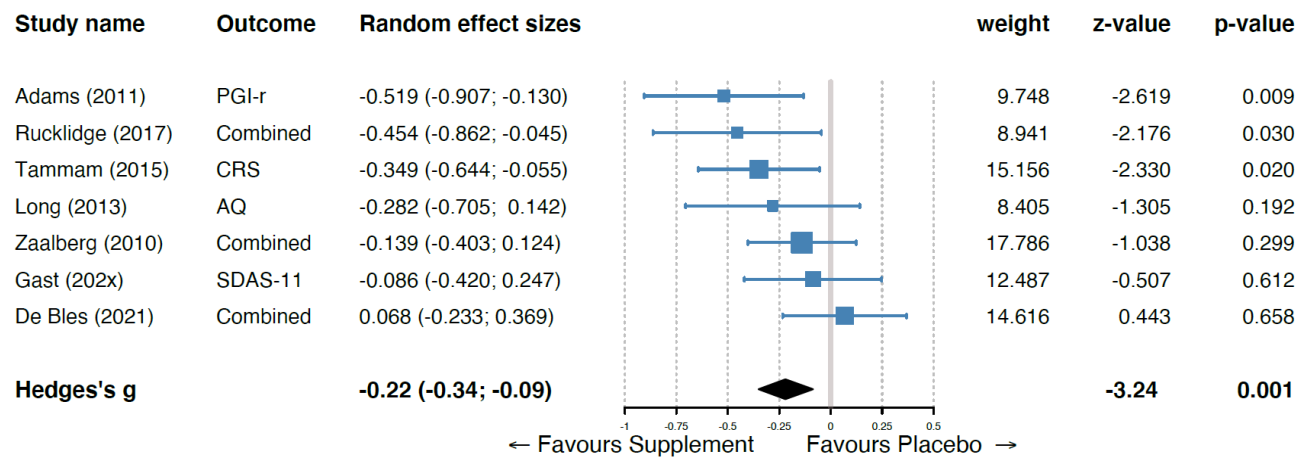

Figure 6.3. Effect sizes (Hedges' *g*) of studies with continuous outcome measures.

Heterogeneity

To explore sources of heterogeneity, we performed a sensitivity analysis by calculating both the random and the fixed effect. For the count data, the degree of statistical heterogeneity was substantial: fixed IRR, 0.64, 95% CI [0.59, 0.70]; and random IRR, 0.72, 95% CI [0.56, 0.93]. The high risk of heterogeneity was confirmed by $I^2 = 84.35$, $Q(7) = 44.72$, $p < .001$. In the case of the continuous data, there was only a small difference between the fixed Hedges' *g*, -0.22, 95% CI [-0.34, -0.09], and random Hedges' *g*, -0.23, 95% CI [-0.38, -0.07], indicating acceptable statistical heterogeneity. The lower risk of heterogeneity was also confirmed by $I^2 = 32.13$, $Q(6) = 8.84$, $p = .18$.

Risk of bias

	Random sequence generation	Allocation Concealment	Blinding of participants	Blinding of outcome data	Incomplete outcome data	Selective reporting	Other bias	Over all bias
Adams (2011)	2	2	1	1	2	2	2	2
De Bles (2021)	1	1	1	2	1	1	1	1
Gast (2021)	1	1	1	1	1	2	2	2
Gesch (2002)	1	1	1	1	2	2	1	2
Long (2013)	1	1	3	2	2	2	2	3
Rucklidge (2018)	1	1	1	1	1	2	2	2
Schoenth. (1997)	2	2	1	2	2	2	2	2
Schoenth. (2000)	2	2	1	2	3	2	3	3
Schoenth. (2021)	1	1	1	1	2	2	2	2
Tammam (2016)	1	1	3	1	1	2	2	3
Zaalberg (2010)	2	1	3	1	2	2	2	3

Figure 6.4. Risk of bias

Figure 6.4 shows the results of the risk of bias assessment. Overall, the risk of bias was substantial: Four trials showed a high level of bias, seven trials showed inconclusive levels, and one trial had a low risk of bias. The greatest risks of bias were insufficient blinding, incomplete outcome data, and selective reporting. Other risks of bias were the COVID-19 pandemic during the cross-over phase of the research (Gast et al., 2022) and using an experimental statistical analysis (Schoenthaler & Bier, 2000). Selective reporting was present in all but one of the trials (De Bles et al., 2022).

Publication bias

The funnel plot of the SE by IRR in Figure 6.5 was not symmetrical, and three studies fell outside the 95% CI. However, the Egger test did not indicate a substantially increased risk of publication bias, 3.14, 95% CI [-1.78, 8.10], p = .17. Given the distribution of the trials over the funnel plot, the asymmetry does not appear to be caused by small trials with large effect sizes but by the variation in trial outcomes with relatively many participants. The funnel plot of the SE by Hedges' g (Figure 6.5) was fairly symmetrical and did not indicate publication bias. This is supported by the results of the Egger test, which showed no significance, -3.68, 95% CI [-10.16, 2.79], p = .20. The various test results have shown that the risk of publication bias was small.

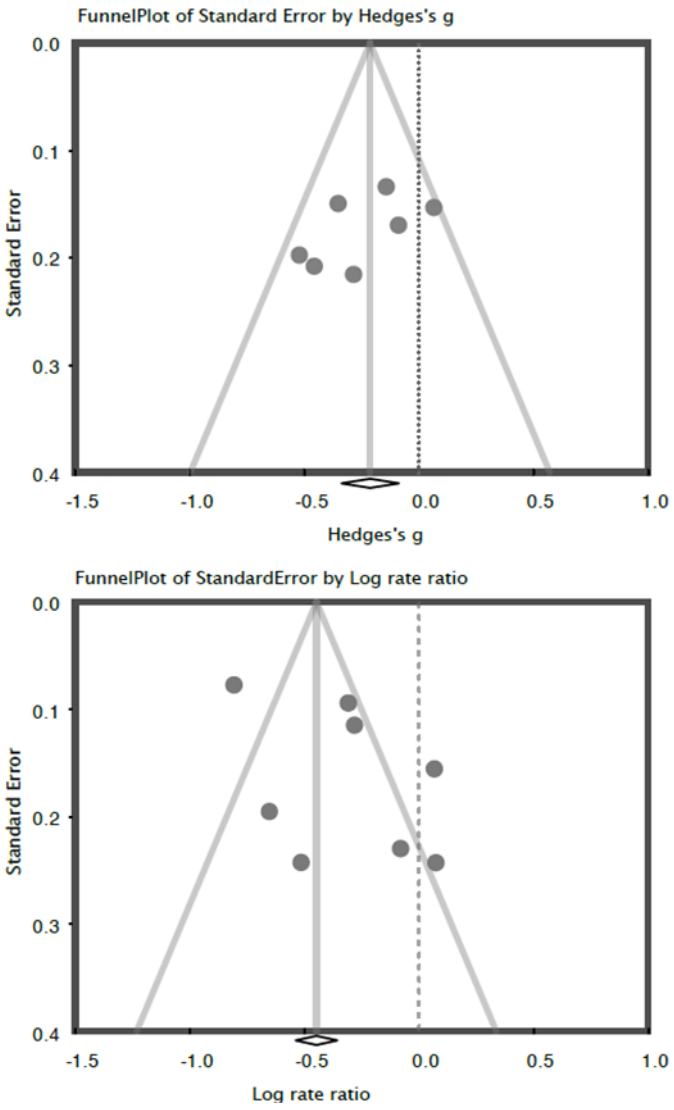

Figure 6.5 Funnel plot of SE by Hedges' g and IRR

Safety

Serious adverse events were not reported in any of the trials. The mild adverse events reported included gastrointestinal symptoms such as nausea, headache, sleeping problems, fatigue, rash, nosebleeds, and psychological symptoms. These adverse events were not significantly more common in the active condition compared to the control group—one exception was the burping of a foul odor in one trial, probably due to omega-3 FA (De Bles et al., 2022).

DISCUSSION

In the present meta-analysis, we included eleven trials and calculated two pooled effect sizes. For the count data outcome, the pooled IRR from eight trials was 0.72, p = .011, which can be interpreted as 28% fewer incidents in the group of active supplements compared to the placebo group. Hedges' g from ten pooled effect sizes of the continuous data was -0.23, p < .004.

The result of this meta-analysis showed a small effect of vitamins and minerals on aggression incidents. Though no meta-analysis has been performed on the effect of multivitamins and minerals on aggression, our conclusions corroborate those of two other meta-analyses on the effect of dietary supplements on problem of behavior. Latter trials used more stringent inclusion criteria. As a result, these trials could examine a more homogeneous study population but were unable to include enough trials to calculate a pooled effect size (Johnstone et al., 2020; Qureshi et al., 2021). Our meta-analysis included more trials by collecting additional information about the outcome data (see Sections 3.1 and 3.2). Another comparable meta-analysis is the study by Gajos and Beaver (2016) on the effect of omega-3 FAs on aggression, which included 30 trials. Their pooled Hedges' g (random effect) was -0.24, which is close to the effect size from our study.

Heterogeneity

In the Results section, we found a difference in heterogeneity between the count data (I^2 = 84.35) and continuous outcome (I^2 = 32.13). Heterogeneity of effect sizes for the count data was relatively high, which could be the result of a smaller number of subjects included in these trials and the different measures and designs. A higher homogeneity of the trial designs, composition and dosages of supplements, and exclusion of behavioral medication would likely have ensured a higher internal validity.

Measuring aggressive behavior

There are many operational definitions of aggression with associated measuring instruments (Parrott & Giancola, 2007; Suris et al., 2004). In addition, aggression has a large overlap with other constructs such as antisocial behavior, challenging behavior, disruptive behavior, externalizing behavior, and violence. By utilizing a broad definition of aggression, we were able to investigate whether there was an effect on aggression in the broadest sense of the word (in terms of aggression topography and characteristics of included samples and settings). Furthermore, we did not select a specific research population, but included all target groups. The individual trials selected their participants using the following inclusion categories, among others: age (Tammam et al., 2016), prison or school setting (Schoenthaler et al., 2021), psychiatric diagnosis (Adams, 2015; De Bles et al., 2022; Rucklidge et al., 2018), people with ID (Gast et al., 2022). Follow-up trials are needed to explore whether differential effects can be found in different target groups, and subtypes of aggression related behavior.

Strength and limitations

The strength of our study is the inclusion of relatively many studies on the effect of supplements on aggressive behavior. However, this meta-analysis also comes with serious limitations. Firstly, uncertainty about the quality of the trials. Only one RCT featured a low risk of bias (De Bles et al., 2022), and it had a null finding. The risks of bias included imperfect blinding and selective reporting. Including trial results with high risk of bias may lead to the quality of evidence being lower than if these trials were excluded. The question therefore remains whether studies with stronger designs would find the same effect than the studies we used in the meta-analysis. Secondly, we used a broad definition of aggressive behavior as inclusion criterium. The outcome measures of the different studies overlapped but were also partly different. For example, rule-offending behavior in prison (e.g., behavior involving substance use or possession of a mobile telephone) may not be related to aggression. Another limitation is that several outcome measures had to be recalculated; for example, we had to combine two intervention arms. These recalculations may have changed the standard error of the effect size estimate, thereby affecting the weight of the trial in the pooled effect size calculation. However, the effect of this recalculation was conservative in nature and may have resulted in a slightly smaller effect size. Finally, the effect has been studied in young and mainly male population, so more research in adults older than 25 years and women is needed.

Future studies

An efficient, safe, affordable, and easy-to-implement intervention is needed in a number of settings and populations. Examples of these subgroups are people with intellectual disabilities, psychiatric patients, male adolescents, and young adult prisoners. For the first two target groups, the evidence of efficacy of supplements is lacking or less clear. Due to the great diversity and the limited number of trials, we could not perform subgroup analyses. The quality of evidence is still largely inconclusive, due to uncertainty about the risk of bias in many trials. Therefore, additional high-quality RCTs are needed. In view of the minor safety risks of this intervention, this meta-analysis would support a high quality Phase 4 trial of the intervention with multivitamins, minerals, and omega-3 FAs supplements. Whether such beneficial effects could also be reached with a healthier and more balanced diet needs to be explored.

Conclusion

Multivitamin/mineral supplements versus placebo showed a small but significant pooled beneficial effect size on aggressive behavior. Due to heterogeneity in the data and a large uncertainty about the risk of bias, these results will have to be replicated in good quality intervention studies.

REFERENCES

1. Adams, J. B. (2015). Vitamin/Mineral Supplements for Children and Adults with Autism. *Vitamins & Minerals, 04*(01). doi:10.4172/2376-1318.1000127
2. Adams, J. B., Audhya, T., McDonough-Means, S., Rubin, R. A., Quig, D., Geis, E., . . . Lee, W. (2011). Effect of a vitamin/mineral supplement on children and adults with autism. *BMC Pediatrics, 11*, 111. doi:10.1186/1471-2431-11-111
3. Bader, S., Evans, S. E., & Welsh, E. (2014). Aggression among psychiatric inpatients: The relationship between time, place, victims, and severity ratings. *Journal of the American Psychiatric Nurses Association, 20*(3), 179-186.
4. Bandura, A. (1973). *Aggression: A social learning analysis*: prentice-hall.
5. Bent, S., Bertoglio, K., & Hendren, R. L. (2009). Omega-3 fatty acids for autistic spectrum disorder: a systematic review. *J Autism Dev Disord, 39*(8), 1145-1154. doi:10.1007/s10803-009-0724-5
6. Benton, D. (2007). The impact of diet on anti-social, violent and criminal behaviour. *Neuroscience & Biobehavioral Reviews, 31*(5), 752-774.
7. Bowring, D. L., Painter, J., & Hastings, R. P. (2019). Prevalence of Challenging Behaviour in Adults with Intellectual Disabilities, Correlates, and Association with Mental Health. *Current Developmental Disorders Reports, 6*(4), 173-181. doi:10.1007/s40474-019-00175-9
8. Bozzatello, P., Brignolo, E., De Grandi, E., & Bellino, S. (2016). Supplementation with Omega-3 Fatty Acids in Psychiatric Disorders: A Review of Literature Data. *J Clin Med, 5*(8). doi:10.3390/jcm5080067
9. Bryant, F. B., & Smith, B. D. (2001). Refining the Architecture of Aggression: A Measurement Model for the Buss–Perry Aggression Questionnaire. *Journal of Research in Personality, 35*(2), 138-167. doi:10.1006/jrpe.2000.2302
10. Buss, A. H., & Perry, M. (1992). The aggression questionnaire. *Journal of personality and social psychology, 63*(3), 452.
11. Calderon-Ospina, C. A., & Nava-Mesa, M. O. (2020). B Vitamins in the nervous system: Current knowledge of the biochemical modes of action and synergies of thiamine, pyridoxine, and cobalamin. *CNS Neuroscience & Therapeutics 26*(1), 5-13. doi:10.1111/cns.13207
12. Choi, Y., Lee, S., Kim, S., Lee, J., Ha, J., Oh, H., . . . Yoon, Y. (2020). Vitamin E (alpha-tocopherol) consumption influences gut microbiota composition. *Int J Food Sci Nutr, 71*(2), 221-225. doi:10.1080/09637486.2019.1639637
13. Choy, O., & Raine, A. (2018). Omega-3 Supplementation as a Dietary Intervention to Reduce Aggressive and Antisocial Behavior. *Curr Psychiatry Rep, 20*(5), 32. doi:10.1007/s11920-018-0894-y
14. Clarivate. (2019). Endnote (Version X9). Philadelphia: Web of Science.
15. Conners, C. K., Sitarenios, G., Parker, J. D., & Epstein, J. N. (1998). The revised Conners' Parent Rating Scale (CPRS-R): factor structure, reliability, and criterion validity. *Journal of abnormal child psychology, 26*(4), 257-268.
16. Cooper, R. E., 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. *Journal of Affective Disorders, 190*, 474-482. doi:10.1016/j.jad.2015.09.053
17. De Bles, N., Rius-Ottenheim, N., Geleijnse, J., Van de Rest, O., Bogers, J., Nijman, H., . . . Giltay, E. (2022). Multivitamin, mineral and n-3 PUFA supplementation to reduce aggression among chronically admitted psychiatric patients: a randomized clinical trial. *BJ Psychiatry Open, 8*(2), E42.
18. Didden, R., Lindsay, W. R., Lang, R., Sigafoos, J., Deb, S., Wiersma, J., . . . Lancioni, G. E. (2016). Aggressive behavior. In N. N. Singh (Ed.), *Handbook of Evidence-Based Practices in Intellectual and Developmental Disabilities* (pp. 727-750): Springer.
19. Emerson, E., Kiernan, C., Alborz, A., Reeves, D., Mason, H., Swarbrick, R., . . . Hatton, C. (2001). The prevalence of challenging behaviors: A total population study. *Research in developmental disabilities, 22*(1), 77-93.
20. Frensham, L. J., Bryan, J., & Parletta, N. (2012). Influences of micronutrient and omega-3 fatty acid supplementation on cognition, learning, and behavior: methodological considerations and implications for children and adolescents in developed societies. *Nutrition Reviews, 70*(10), 594-610.

21. Fritz, C. O., Morris, P. E., & Richler, J. J. (2012). Effect size estimates: current use, calculations, and interpretation. *J Exp Psychol Gen, 141*(1), 2-18. doi:10.1037/a0024338
22. Gajos, J. M., & Beaver, K. M. (2016). The effect of omega-3 fatty acids on aggression: A meta-analysis. *Neuroscience & Biobehavioral Reviews, 69*, 147-158.
23. Gast, D. A. A., Didden, R., Westera, J. J., Van de Rest, O., Van Hemert, A. M., & Giltay, E. J. (2022). Do Dietary Supplements Reduce Aggressive Behavior in People With Intellectual Disabilities? A Randomized Controlled Trial. *(Submitted)*.
24. Gesch, C. B. (2011). *The Influence of Micronutrient Intake on Antisocial Behaviours.* (PhD), University College, Cork.
25. Gesch, C. B., Hammond, S. M., Hampson, S. E., Eves, A., & Crowder, M. J. (2002). Influence of supplementary vitamins, minerals and essential fatty acids on the antisocial behaviour of young adult prisoners. Randomised, placebo-controlled trial. *British Journal of Psychiatry, 181*(1), 22-28. doi:10.1192/bjp.181.1.22
26. Goodman, R. (2001). Psychometric properties of the strengths and difficulties questionnaire. *Journal of the American Academy of Child & Adolescent Psychiatry, 40*(11), 1337-1345.
27. Gould, J. F., Roberts, R. M., & Makrides, M. (2021). The Influence of Omega-3 Long-Chain Polyunsaturated Fatty Acid, Docosahexaenoic Acid, on Child Behavioral Functioning: A Review of Randomized Controlled Trials of DHA Supplementation in Pregnancy, the Neonatal Period and Infancy. *Nutrients, 13*(2). doi:10.3390/nu13020415
28. Hambly, J. L., Francis, K., Khan, S., Gibbons, K. S., Walsh, W. J., Lambert, B., . . . Haywood, A. (2017). Micronutrient Therapy for Violent and Aggressive Male Youth: An Open-Label Trial. *J Child Adolesc Psychopharmacol, 27*(9), 823-832. doi:10.1089/cap.2016.0199
29. Hedges, L. V. (1986). Issues in Meta-Analysis. *Research in Education, 13*(1), 353-398.
30. Hensel, J. M., Lunsky, Y., & Dewa, C. S. (2012). Exposure to client aggression and burnout among community staff who support adults with intellectual disabilities in Ontario, Canada. *Journal of Intellectual Disability Research, 56*(9), 910-915.
31. Higgins, J. P., Altman, D. G., Gøtzsche, P. C., Jüni, P., Moher, D., Oxman, A. D., . . . Sterne, J. A. (2011). The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *Bmj, 343*, d5928.
32. Higgins, J. P., & Green, S. (2011). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1. 0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www. cochrane-handbook. org. *Accessed August, 29*.
33. Jin, Z.-C., Zhou, X.-H., & He, J. (2015). Statistical methods for dealing with publication bias in meta-analysis. *Statistics in Medicine, 34*(2), 343-360. doi:10.1002/sim.6342
34. Johnstone, J. M., Hughes, A., Goldenberg, J. Z., Romijn, A. R., & Rucklidge, J. J. (2020). Multinutrients for the Treatment of Psychiatric Symptoms in Clinical Samples: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Nutrients, 12*(11). doi:10.3390/nu12113394
35. Kennedy, D. O. (2016). B Vitamins and the Brain: Mechanisms, Dose and Efficacy--A Review. *Nutrients, 8*(2), 68. doi:10.3390/nu8020068
36. Lee, A. H., & DiGiuseppe, R. (2018). Anger and aggression treatments: a review of meta-analyses. *Curr Opin Psychol, 19*, 65-74. doi:10.1016/j.copsyc.2017.04.004
37. Liu, J., Liu, X., Xiong, X. Q., Yang, T., Cui, T., Hou, N. L., . . . Li, T. Y. (2017). Effect of vitamin A supplementation on gut microbiota in children with autism spectrum disorders - a pilot study. *BMC Microbiol, 17*(1), 204. doi:10.1186/s12866-017-1096-1
38. Lloyd, B. P., & Kennedy, C. H. (2014). Assessment and treatment of challenging behaviour for individuals with intellectual disability: A research review. *Journal of Applied Research in Intellectual Disabilities, 27*(3), 187-199.
39. Long, S. J., & Benton, D. (2013). A double-blind trial of the effect of docosahexaenoic acid and vitamin and mineral supplementation on aggression, impulsivity, and stress. *Human Psychopharmacology: Clinical and Experimental, 28*(3), 238-247. doi:10.1002/hup.2313
40. Luthold, R. V., Fernandes, G. R., Franco-de-Moraes, A. C., Folchetti, L. G., & Ferreira, S. R. (2017). Gut microbiota interactions with the immunomodulatory role of vitamin D in normal individuals. *Metabolism, 69*, 76-86. doi:10.1016/j.metabol.2017.01.007
41. Messina, M., Lampe, J. W., Birt, D. F., & Appel, L. J. (2001). Reductionism and the narrowing nutrition perspective: time for reevaluation and emphasis on food synergy. *Journal of the Academy of Nutrition and Dietetics, 101*(12), 1416-1419.
42. Needham, I., Abderhalden, C., Halfens, R. J., Fischer, J. E., & Dassen, T. (2005). Non-somatic effects of patient aggression on nurses: a systematic review. *Journal of advanced nursing, 49*(3), 283-296.

43. Nijman, H. L., Muris, P., Merckelbach, H. L., Palmstierna, T., Wistedt, B., Vos, A., . . . Allertz, W. (1999). The staff observation aggression scale–revised (SOAS-R). *Aggressive Behavior: Official Journal of the International Society for Research on Aggression, 25*(3), 197-209.
44. O'Rourke, M. M. (1994). *Anger: Its measurement and Implications for Treatment.* (PhD), University of Surrey,
45. Oliver, P., Crawford, M., Rao, B., Reece, B., & Tyrer, P. (2007). Modified Overt Aggression Scale (MOAS) for people with intellectual disability and aggressive challenging behaviour: a reliability study. *Journal of Applied Research in Intellectual Disabilities, 20*(4), 368-372.
46. Parletta, N., Milte, C. M., & Meyer, B. J. (2013). Nutritional modulation of cognitive function and mental health. *The Journal of Nutritional Biochemistry, 24*(5), 725-743.
47. Parrott, D. J., & Giancola, P. R. (2007). Addressing "The criterion problem" in the assessment of aggressive behavior: Development of a new taxonomic system. *Aggression and Violent Behavior, 12*(3), 280-299. doi:10.1016/j.avb.2006.08.002
48. Qureshi, F. M., Kunaratnam, N., Kolla, N. J., & Konkoly Thege, B. (2021). Nutritional supplementation in the treatment of violent and aggressive behavior: A systematic review. *Aggress Behav, 47*(3), 296-309. doi:10.1002/ab.21953
49. Rucker, G., Cates, C. J., & Schwarzer, G. (2017). Methods for including information from multi-arm trials in pairwise meta-analysis. *Res Synth Methods, 8*(4), 392-403. doi:10.1002/jrsm.1259
50. Rucklidge, J. J., Eggleston, M. J. F., Johnstone, J. M., Darling, K., & Frampton, C. M. (2018). Vitamin-mineral treatment improves aggression and emotional regulation in children with ADHD: a fully blinded, randomized, placebo-controlled trial. *Journal of Child Psychology and Psychiatry, 59*(3), 232-246. doi:10.1111/jcpp.12817
51. Rucklidge, J. J., & Kaplan, B. J. (2013). Broad-spectrum micronutrient formulas for the treatment of psychiatric symptoms: a systematic review. *Expert Review of Neurotherapeutics, 13*(1), 49-73.
52. Schoenthaler, S. J., Amos, W., Doraz, M.-A., Kelly, G., Muedeking, J., & Wakefield, S. j. (1997). The effect of randomized vitamin-mineral supplementation on violent and non-violent antisocial behavior among incarcerated juveniles. *Journal of Nutritional and Environmental Medicine, 7*(4), 343-352.
53. Schoenthaler, S. J., & Bier, I. D. (2000). The effect of vitamin-mineral supplementation on juvenile delinquincy among American schoolchildren: A randomized, double-blind placebo-controlled trial. *The Journal of Alternative and Complementary Medicine, 6*(1), 7-17.
54. Schoenthaler, S. J., Gast, D. A. A., Giltay, E. J., & Amos, S. P. (2021). The Effects of VitaminMineral Supplements on Serious Rule Violations in Correctional Facilities for Young Adult Male Inmates: A Randomized Controlled Trial. *Crime & Delinquency*.
55. Steiner, B., & Cain, M. C. (2016). The Relationship Between Inmate Misconduct, Institutional Violence, and Administrative Segregation: A Systematic Review of the Evidence. In E. L. Lynch, K. V. Mason, & N. Rodriguez (Eds.), *Restrictive Housing in the U.S. Issues, Challenges, and Future Directions*. Washington: National Institute of justice.
56. Sullivan, K. M., Dean, A., & Soe, M. M. (2009). On academics: OpenEpi: a web-based epidemiologic and statistical calculator for public health. *Public health reports, 124*(3), 471-474.
57. Suris, A., Lind, L., Emmett, G., Borman, P. D., Kashner, M., & Barratt, E. S. (2004). Measures of aggressive behavior: overview of clinical and research instruments. *Aggression and Violent Behavior, 9*(2), 165-227.
58. Tammam, J., Steinsaltz, D., Bester, D. W., Semb-Andenaes, T., & Stein, J. (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. *The British Journal of Nutrition, 115*(2), 361-373.
59. Wistedt, B., Rasmussen, A., Pedersen, L., Malm, U., Träskman-Bendz, L., Wakelin, J., & Bech, P. (1990). The development of an observer-scale for measuring social dysfunction and aggression. *Pharmacopsychiatry, 23*(6), 249-252.
60. Zaalberg, A., Nijman, H., Bulten, E., Stroosma, L., & Van Der Staak, C. (2010). Effects of nutritional supplements on aggression, rule-breaking, and psychopathology among young adult prisoners. *Aggressive Behavior: Official Journal of the International Society for Research on Aggression, 36*(2), 117-126.

APPENDIX

Search strings within the various databases:

Pubmed

("Omega-3"[tw] OR "fatty acids"[tw] OR "fatty acid"[tw] OR "n3"[tw] OR "n-3"[tw] OR "PUFA"[tw] OR "Fish Oils"[tw] OR "Fish Oil"[tw] OR "Dietary Supplements"[tw] OR "Dietary Supplement"[tw] OR "Dietary Supplementation"[tw] OR "Dietary Supplementations"[tw] OR "Food Supplements"[tw] OR "Food Supplement"[tw] OR "food supplementation"[tw] OR "food supplementations"[tw] OR "Nutraceutical"[tw] OR "Nutraceuticals"[tw] OR "Nutriceutical"[tw] OR "Nutriceuticals"[tw] OR "Vitamins"[tw] OR "Vitamin"[tw] OR "Vitamins" OR "Cholecalciferol"[tw] OR "Niacin"[tw] OR "Niacinamine"[tw] OR "Niacinamin"[tw] OR "Niacinamide"[tw] OR "Pyridoxal"[tw] OR "Pyridoxamine"[tw] OR "Pyridoxamin"[tw] OR "Pyridoxine"[tw] OR "Folic Acid"[tw] OR "Folic Acids"[tw] OR "multivitamin"[tw] OR "multivitamins"[tw] OR "megavitamin"[tw] OR "megavitamins"[tw] OR "Minerals"[tw] OR "Mineral"[tw] OR "Selenium"[tw] OR "micronutrients"[tw] OR "micronutrition"[tw] OR "micronutritional"[tw] OR "micronutrient"[tw] OR "micro nutrients"[tw] OR "micro nutrition"[tw] OR "micro nutritional"[tw] OR "micro nutrient"[tw]) AND ("Externalizing Behavior"[tw] OR "Externalising Behaviour"[tw] OR "external behaving"[tw] OR "antisocial Behavior"[tw] OR "antisocial Behaviour"[tw] OR "antisocial behaving"[tw] OR "aggression"[tw] OR "aggressive"[tw] OR "Self-Control"[tw] OR "selfcontrol"[tw] OR "self controlling"[tw] OR "selfcontrolling"[tw] OR "behavior problem"[tw] OR "behaviour problem"[tw] OR "behavior problems"[tw] OR "behaviour problems"[tw] OR "Impulsive Behavior"[tw] OR "Impulsive Behaviour"[tw] OR "Impulsive Behaviors"[tw] OR "Impulsive Behaviours"[tw] OR "impulsiveness"[tw] OR "Impulsivity"[tw] OR "Impulsivities"[tw] OR "Mood Disorders"[tw] OR "Mood Disorder"[tw] OR "Affective Disorder"[tw] OR "Affective Disorders"[tw] OR "Irritable Mood"[Mesh] OR "Irritable Mood"[tw] OR "Irritable Moods"[tw] OR "Conduct Disorder"[tw] OR "Conduct Disorders"[tw] OR "Violence"[tw] OR "Violent"[tw] OR "Assaultive Behavior"[tw] OR "Assaultive Behaviour"[tw] OR "Assaultive Behaviors"[tw] OR "Assaultive Behaviours"[tw] OR "Assaultive Behaving"[tw] OR "Assaultive Behaving"[tw] OR "socially non-acceptable"[tw] OR "hostility"[tw] OR "hostilities"[tw] OR "hostile"[tw]) AND (“trial” [tw] OR “rct” [tw])

WoS:

TS=("Fatty Acids, Omega-3" OR "Omega-3" OR "fatty acids" OR "fatty acid" OR "n3" OR "n-3" OR "PUFA" OR "Fish Oils" OR "Fish Oils" OR "Fish Oil" OR "Dietary Supplements" OR "Dietary Supplements" OR "Dietary Supplement" OR "Dietary Supplementation" OR "Dietary Supplementations" OR "Food Supplements" OR "Food Supplement" OR "food supplementation" OR "food supplementations" OR "Nutraceutical" OR "Nutraceuticals" OR "Nutriceutical" OR "Nutriceuticals" OR "Vitamins" OR "Vitamins" OR "Vitamin" OR "Vitamins" OR "Cholecalciferol" OR "Niacin" OR "Niacinamine" OR "Niacinamin" OR "Niacinamide" OR "Pyridoxal" OR "Pyridoxamine" OR "Pyridoxamin" OR "Pyridoxine" OR "Folic Acid" OR "Folic Acids" OR "multivitamin" OR "multivitamins" OR "megavitamin" OR "megavitamins" OR "Minerals" OR "Selenium" OR "Minerals" OR "Mineral" OR "Selenium" OR "micronutrients" OR "micronutrition" OR "micronutritional" OR "micronutrient" OR "micro nutrients" OR "micro nutrition" OR "micro nutritional" OR "micro nutrient") AND TS=("Externalizing Behavior" OR "Externalising Behaviour" OR "antisocial behaving" OR "aggression" OR "aggressive" OR "Self-Control" OR "selfcontrol" OR "self controlling" OR "selfcontrolling" OR "behavior problem" OR "behaviour problem" OR "behavior problems" OR "behaviour problems" OR "Impulsive Behavior" OR "Impulsive Behaviour" OR "Impulsive Behaviors" OR "Impulsive Behaviours" OR "impulsiveness" OR "Impulsivity" OR "Impulsivities" OR "Mood Disorders" OR "Mood Disorders" OR "Mood Disorder" OR "Affective Disorder" OR "Affective Disorders" OR "Irritable Mood" OR "Irritable Mood" OR "Irritable Moods" OR "Conduct Disorder" OR "Conduct Disorder" OR "Conduct Disorders" OR "Violence" OR "Violence" OR "Violent" OR "Assaultive Behavior" OR "Assaultive Behaviour" OR "Assaultive Behaviors" OR "Assaultive Behaviours" OR "Assaultive Behaving" OR "Assaultive Behaving" OR "socially non-acceptable" OR "hostility" OR "hostilities" OR "hostile") AND TS=(“Trials” OR “rct”)

EMBASE

("Fatty Acids, Omega-3" OR "Omega-3" OR "fatty acids" OR "fatty acid" OR "n3" OR "n-3" OR "PUFA" OR "Fish Oils" OR "Fish Oils" OR "Fish Oil" OR "Dietary Supplements" OR "Dietary Supplements" OR "Dietary Supplement" OR "Dietary Supplementation" OR "Dietary Supplementations" OR "Food Supplements" OR "Food Supplement" OR "food supplementation" OR "food supplementations" OR "Nutraceutical" OR "Nutraceuticals" OR "Nutriceutical" OR "Nutriceuticals" OR "Vitamins" OR "Vitamins" OR "Vitamin" OR "Vitamins" OR "Cholecalciferol" OR "Niacin" OR "Niacinamine" OR "Niacinamin" OR "Niacinamide" OR "Pyridoxal" OR "Pyridoxamine" OR "Pyridoxamin" OR "Pyridoxine" OR "Folic Acid" OR "Folic Acids" OR "multivitamin" OR "multivitamins" OR "megavitamin" OR "megavitamins" OR "Minerals" OR "Selenium" OR "Minerals" OR "Mineral" OR "Selenium" OR "micronutrients" OR "micronutrition" OR "micronutritional" OR "micronutrient" OR "micro nutrients" OR "micro nutrition" OR "micro nutritional" OR "micro nutrient") AND ("Externalizing Behavior" OR " Externalising Behaviour" OR "antisocial behaving" OR "aggression" OR "aggressive" OR "Self-Control" OR "selfcontrol" OR "self controlling" OR "selfcontrolling" OR "behavior problem" OR "behaviour problem" OR "behavior problems" OR "behaviour problems" OR "Impulsive Behavior" OR "Impulsive Behaviour" OR "Impulsive Behaviors" OR "Impulsive Behaviours" OR "impulsiveness" OR "Impulsivity" OR "Impulsivities" OR "Mood Disorders" OR "Mood Disorders" OR "Mood Disorder" OR "Affective Disorder" OR "Affective Disorders" OR "Irritable Mood" OR "Irritable Mood" OR "Irritable Moods" OR "Conduct Disorder" OR "Conduct Disorder" OR "Conduct Disorders" OR "Violence" OR "Violence" OR "Violent" OR "Assaultive Behavior" OR "Assaultive Behaviour" OR "Assaultive Behaviors" OR "Assaultive Behaviours" OR "Assaultive Behaving" OR "Assaultive Behaving" OR "socially non-acceptable" OR "hostility" OR "hostilities" OR "hostile") AND ("trial" OR "rct")

PsycInfo

("Fatty Acids, Omega-3" OR "Omega-3" OR "fatty acids" OR "fatty acid" OR "n3" OR "n-3" OR "PUFA" OR "Fish Oils" OR "Fish Oils" OR "Fish Oil" OR "Dietary Supplements" OR "Dietary Supplements" OR "Dietary Supplement" OR "Dietary Supplementation" OR "Dietary Supplementations" OR "Food Supplements" OR "Food Supplement" OR "food supplementation" OR "food supplementations" OR "Nutraceutical" OR "Nutraceuticals" OR "Nutriceutical" OR "Nutriceuticals" OR "Vitamins" OR "Vitamins" OR "Vitamin" OR "Vitamins" OR "Cholecalciferol" OR "Niacin" OR "Niacinamine" OR "Niacinamin" OR "Niacinamide" OR "Pyridoxal" OR "Pyridoxamine" OR "Pyridoxamin" OR "Pyridoxine" OR "Folic Acid" OR "Folic Acids" OR "multivitamin" OR "multivitamins" OR "megavitamin" OR "megavitamins" OR "Minerals" OR "Selenium" OR "Minerals" OR "Mineral" OR "Selenium" OR "micronutrients" OR "micronutrition" OR "micronutritional" OR "micronutrient" OR "micro nutrients" OR "micro nutrition" OR "micro nutritional" OR "micro nutrient") AND ("Externalizing Behavior" OR " Externalising Behaviour" OR "antisocial behaving" OR "aggression" OR "aggressive" OR "Self-Control" OR "selfcontrol" OR "self controlling" OR "selfcontrolling" OR "behavior problem" OR "behaviour problem" OR "behavior problems" OR "behaviour problems" OR "Impulsive Behavior" OR "Impulsive Behaviour" OR "Impulsive Behaviors" OR "Impulsive Behaviours" OR "impulsiveness" OR "Impulsivity" OR "Impulsivities" OR "Mood Disorders" OR "Mood Disorders" OR "Mood Disorder" OR "Affective Disorder" OR "Affective Disorders" OR "Irritable Mood" OR "Irritable Mood" OR "Irritable Moods" OR "Conduct Disorder" OR "Conduct Disorder" OR "Conduct Disorders" OR "Violence" OR "Violence" OR "Violent" OR "Assaultive Behavior" OR "Assaultive Behaviour" OR "Assaultive Behaviors" OR "Assaultive Behaviours" OR "Assaultive Behaving" OR "Assaultive Behaving" OR "socially non-acceptable" OR "hostility" OR "hostilities" OR "hostile") AND ("trial" OR "rct")