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Omega-3 supplementation in young offenders: a randomized, stratified, double-blind, placebo-controlled, parallel-group trial

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Abstract

Objectives To examine whether omega-3 supplementation reduces antisocial and aggressive behavior in offenders.
Methods In this randomized, double-blind trial, 145 young offenders were randomized into three groups: omega-3 ($N = 48$), placebo ($N = 46$), and treatment-as-usual controls ($N = 51$). Measures of antisocial, aggressive, and psychopathic behavior were collected at 0 months (baseline), 3 months (end of treatment), 6 months (3 months post-treatment), and 12 months (9 months post-treatment).
Results Omega-3 supplementation resulted in both short-term and long-term declines in self-reported antisocial and aggressive behavior. Findings were stronger for a reactive-impulsive form of aggression than for proactive aggression and psychopathy. Sensitivity analyses documented long-term reductions at 6 and 12 months in the omega-3 group for officer reports.
Conclusions Results suggest that omega-3 supplementation can help reduce antisocial and aggressive behavior over and above regular treatment programs in young offender institutions, particularly for reactive, impulsive aggression.

Keywords Omega-3 · Antisocial · Reactive aggression · Offenders · Psychopathy · Randomized controlled trial

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Introduction

There is increasing interest in the use of omega-3 as a treatment for aggressive and antisocial behavior. The notion that improved nutrition could reduce antisocial behavior is predicated on risk research documenting that poor nutritional status is a risk factor for externalizing behavior problems and antisocial personality disorder (Liu, Raine, Venables, Dalais, & Mednick, 2004; Neugebauer, Hoek, & Susser, 1999). Omega-3 has been hypothesized as one nutritional component that could explain the link between poor nutrition and antisocial behavior (Raine, Mellingen, Liu, Venables, & Mednick, 2003). Randomized controlled trials (RCTs) have shown some evidence for the efficacy of omega-3 supplementation in reducing antisocial behavior (Raine, Portnoy, Liu, Mahoomed, & Hibbeln, 2015; Raine et al., 2016). Aggressive behavior in particular has been a focus of studies, with a recent meta-analysis of aggression yielding an effect size of $d = 0.24$ (Gajos & Beaver, 2016). As such, there is growing support for a small but significant effect of omega-3 supplementation in reducing antisocial behavior, particularly for aggressive behavior.

From a mechanistic standpoint, there is reason to believe omega-3 could help attenuate neurobiological risk factors for antisocial and aggressive behavior. Animal research has documented that this long-chain fatty acid plays a critical role in brain structure and function, making up approximately 35% of the cell membrane, enhancing neurite outgrowth, and regulating both neurotransmitter functioning and gene expression (McNamara & Carlson, 2006). Structural and functional brain imaging studies on humans have further documented that omega-3 can enhance a variety of brain regions, with no evidence for any detrimental effect (McNamara et al. 2019). Because many of these brain regions overlap with brain areas documented to be impaired in antisocial and violent individuals (Raine 2014), it is reasonable to presume that omega-3 supplementation could help remediate neural risk factors for offending.

Despite progress made in prior studies on omega-3 supplementation for reducing antisocial behavior, two broad questions remain unanswered. The first concerns the form of aggression that omega-3 can attenuate. An important distinction in the literature lies between reactive aggression which is impulsive, emotional, and "hot-blooded," and proactive aggression which is planned, regulated, and "cold-blooded" (Scarpa, Haden, & Tanaka, 2010). To the extent that omega-3 has been shown to reduce impulsive behavior, omega-3 supplementation may be more efficacious for reactive, impulsive aggression. Only three omega-3 RCT intervention studies have addressed this question. The first from Mauritius documented significant reductions in both forms of aggression (Raine et al., 2015). The second RCT from the USA documented significant reductions in reactive but not proactive aggression (Raine et al., 2016), while the third RCT from Singapore replicated the significant reductions in reactive but not proactive aggression (Raine et al. 2019). Omega-3 supplementation could therefore be expected to be more effective for reactive than proactive aggression, although support to date is limited and mixed.

A second issue concerns the efficacy of omega-3 for offenders. Only two prior prison studies have addressed this issue. One RCT from England provided omega-3 and omega-6 together with multivitamins and minerals for an average of 142 days (range 2 weeks to 9 months). Compared to a placebo group, the experimental group showed a significant 26.3% reduction in prison offenses (Gesch, Hammond, Hampson,

Eves, & Crowder, 2002), although null effects were found for self-report measures (Gesch, 2011). No measures of officer reports were reported. The second RCT conducted in the Netherlands provided omega-3 and multivitamins over an average of 76 days (range 1 to 3 months), and showed a significant reduction in prison incidents, together with a trend for reduced self-report aggression (Zaalberg, Nijman, Bulten, Stroosma, & van der Staak, 2010).

While these two pioneering studies document for the first time some evidence for the efficacy of omega-3 in offenders, they inevitably have some methodological limitations. Gesch et al. (2002) did not include officer-reports, and the dose of DHA and EPA was small (124 mg). In both studies, there was significant variability in treatment duration from prisoner to prisoner, with durations as short as 2 weeks. No treatment-as-usual control groups were included. Because both studies also provided multivitamins, it cannot be concluded that treatment effects were due to omega-3. Importantly, prisoners were not followed up post-treatment to assess whether treatment effects could be sustained over time. Due to the limited sources of antisocial behavior, they were not able to assess for differential effects on different forms of antisocial behavior (e.g., reactive forms of aggression and psychopathic behavior). Drop-out rates in both studies were non-trivial, with rates of 32.2% in Zaalberg et al. (2009) and 25.5% in Gesch et al. (2002). Despite limitations, these two important but initial studies support the hypothesis that nutritional supplementation has efficacy with young offenders.

The present study attempted to address these gaps in the literature and also to assess generalizability of findings from European countries to a south-east Asian sample. The RCT included three groups (treatment-as-usual controls, placebo, and omega-3), with antisocial behavior assessed from self-reports, officer reports, and prison infractions. It was hypothesized that the omega-3 group would show a reduction in antisocial behavior relative to control groups. It was further hypothesized that any treatment effects may be stronger for more reactive, impulsive aggression.

Methods

Trial design

The design consisted of a randomized, stratified, double-blind, placebo-controlled, parallel-group trial (1:1:1 ratio) of young male offenders. Offenders were randomized into three groups, controls (n = 51), placebo (n = 46), and omega-3 (n = 48), and were assessed at 0 months (start of treatment), 3 months (end of treatment), 6 months (3 months post-treatment), and 12 months (9 months post-treatment). The treatment-as-usual control group was included to assess for any placebo effect as well as the effect of instituting omega-3 supplementation and as such this group was not blinded. Trial design and outcomes remained unchanged throughout the study.

Participants

Eligibility criteria. Participants had to be aged 16 years or older at the time of study, willing to participate in an RCT, and residing in a reformative training center in

Singapore. Exclusion criteria consisted of (1) allergy to fish or fish products, (2) use of omega-3 supplementation in the past 3 months, (3) intellectual disability, and (4) ineligible to enter reformative training. Written informed consent was obtained from participants and in addition for participants below the age of 18, written parental consent was also obtained, with IRB approval from the University of Pennsylvania.

Study setting, location, and registration. The study took place in a secure institution contained in Changi Prison Complex in Singapore. Participants completed questionnaires in a classroom located within the reformative training center. For officer-rated measures, questionnaires were completed at each officer's workspace within the institution. The study was registered in ClinicalTrials.gov (NCT03627312) under the title "Omega-3 Supplements to Reduce Antisocial Behavior in Young Offenders" (https://clinicaltrials.gov/ct2/results?cond=&term=SingaporePS&cntry=&state=&city=&dist).

Omega-3 and standard institutional treatment

Omega-3 supplementation. This consisted of a 200-ml drink (Smartfish Recharge). The base drink in both treatment and placebo conditions consisted of fruit juice from apple, pear, pomegranate, aronia, and passion fruit. It also contained vitamin D (5 μg) and antioxidants (ferric reducing ability of plasma value of 0.71 mmol/100 g). For the treatment condition only, a total of 840 mg of omega-3 (300 mg of DHA, 300 mg of EPA, 180 mg of alpha-linolenic acid, and 60 mg of DPA) was added to the base drink. Placebo drinks were matched exactly with the omega-3 drink in terms of size, appearance, and flavor.

This drink was chosen because (1) it contains an appreciably higher dosage of omega-3 than standard capsules in a relatively small liquid, and (2) a pilot study conducted on the young offenders documented that the fruit-flavored drink was better tolerated and preferred over standard capsules.

Omega-3 treatment duration and administration. Treatment duration was 3 months. The omega-3 drink was administered in the morning before breakfast by the officers on duty.

Omega-3 monitoring. Prison officers monitored the administration of the drinks on a daily basis. They were blind to group assignment and none were part of the research team.

Standard institutional treatment. All three groups received the standard treatment obtained by all young offenders during incarceration. This consisted of academic training, vocational training, religious counseling, a family involvement program, and a community re-integration program. Each inmate was assigned a personal supervisor who provided close guidance and monitoring of the young offender's welfare and behavior.

Outcome measures

Aggression Questionnaire (AQ) (self-report only). The Aggression Questionnaire (Buss & Warren, 2000) produces five subscale scores for physical aggression, verbal aggression, anger, hostility, and indirect aggression. Extensive support has been documented for convergent, discriminant, and factorial validity, including studies of young offenders (Pechorro, Barroso, Poiares, Oliveira, & Torrealday, 2016).

Youth Psychopathic Traits Inventory (YPI) (self-report only). This instrument (Andershed, Kerr, Stattin, & Levander, 2002) yields three psychopathic personality subscales: Grandiose/Manipulative (interpersonal domain), Callous/Unemotional (affective domain), and Impulsive/Irresponsible (lifestyle/behavioral). Reliability and validity have been documented for this scale in young offenders (Cauffman, Kimonis, Dmitrieva, & Monahan, 2009; Pechorro, da Silva, Rijo, Goncalves, & Andershed, 2017).

Reactive-Proactive Aggression Questionnaire (RPQ) (self-report and officer report). Participants completed this self-report instrument which yields scales of reactive, proactive, and total aggression (Raine et al., 2006). Reliability and validity have been documented (Baker, Raine, Liu, & Jacobson, 2008; Fossati et al., 2009; Cima, Raine, Meesters, & Popma, 2013).

Adult Self-Report (ASR) (self-report only). Participants self-reported on Aggressive Behavior and Rule-Breaking Behavior subscales of the ASR (Achenbach, Rescorla, & Ivanova, 2015). Extensive evidence for reliability, validity, and cross-cultural generalizability has been documented in over 100 societies (Achenbach & Rescorla, 2001).

Conduct and Oppositional Defiant Disorder Scales (CODDS) (self-report and officer report). This 23-item measure is modeled on DSM 5 and assesses the eight DSM oppositional defiant disorder criteria and the 15 conduct disorder criteria (Raine et al., 2016), yielding conduct disorder and oppositional defiant disorder scores. Good construct validity for these scales has been documented (Choy, Raine, Venables, & Farrington, 2017; Raine et al., 2019).

The Antisocial Process Screening Device (APSD) (self-report and officer report). This 20-item scale assesses parent- and child-reported psychopathic traits (Frick, Bodin, & Barry, 2000), yielding three subscales of callous-unemotional, narcissism, and impulsivity. Reliability has been reported as good with the exception of the callous-unemotional scale, with good support for the three-factor model (Salekin, Andershed, & Clark, 2018).

Adult Behavior Checklist (ABCL) (officer report only). Officers rated participants on the Aggressive Behavior and Rule-Breaking Behavior subscales of the ABCL (Achenbach et al., 2015). Extensive evidence for reliability, validity, and cross-cultural generalizability has been documented in over 100 societies (Achenbach & Rescorla, 2001).

Social Dysfunction and Aggression Scale (officer report only). This instrument assesses aggressive behavior as measured by observers (Wistedt et al., 1990). The nine-item Outward Aggression subscale was utilized in this study. Acceptable reliability and construct validity have been documented on institutionalized populations (Wistedt et al., 1990; Grube, 2004).

Institutional infractions. Infractions were measured on a standard list grouped by severity into aggravated (e.g., assault or attack on officer), minor (e.g., quarreling with other prisoners), or warning infractions (similar to minor infractions but where a warning is given).

Dimension reduction. To both provide more robust indices of antisocial behavior and to help reduce type 1 error, all self-report and officer-report scales were separately factor analyzed (see Online supplementary material for full details). This resulted in one overall measure of officer-reported antisocial-aggressive behavior, one overall measure of self-report antisocial-aggressive behavior, and

three self-report sub-factors (Reactive-Impulsive Aggression, Psychopathy, and Proactive Aggression-Conduct Disorder).

Blinding success/failure. Participants in the two drink groups were asked at the end of treatment to guess whether they were in the placebo or omega-3 group.

Sample size

Based on prior findings for omega-3 RCTs where the primary outcome was antisocial behavior (Raine, Portnoy, Liu, Mahoomed, & Hibbeln, 2015; Raine et al., 2016), together with results of a meta-analysis of omega-3 RCTs on aggression (Gajos & Beaver, 2016), a small to medium effect size was anticipated. The final total sample size of 145 would have power of 0.80 to detect a small to medium effect size of $f = 0.219$, alpha = 0.05, and critical $F(6,282) = 2.13$.

Randomization and stratification

Participants were randomized into treatment, placebo, and control groups by the research coordinator using Urn randomization (Wei, 1978), stratifying on age (four age bands in years—16, 17, 18, 19 and above), ethnicity (Chinese/Malay/Indian/Others), past violence (yes/no based on current conviction), and violence risk (Low, Low-Moderate, Moderate, Moderate-High, High) based on the Structured Assessment of Violence Risk in Youth (SAVRY—Borum, Bartel, & Forth, 2006).

Blinding

All persons involved in data collection and outcome reporting, including participants, research assistants, and prison officers, were blind to the active/placebo omega-3 group allocation (the treatment-as-usual control group was not blinded). Allocation concealment was maintained by having the omega-3 intervention allocation conducted separately by the project coordinator who was kept independent of participants, investigators, and knowledge of which drink codes were omega-3 or placebo. Coding of the drinks was kept only by the first author at an overseas site who had no contact with study participants and was not involved in data collection.

Statistical methods

An intention-to-treat (ITT) design using all randomly assigned participants without any exclusion was employed for all data analyses, with data missing due to loss at follow-up handled using mixed effects modeling (Molenberghs & Verbeke, 2005). An ITT approach was adopted because it is considered a gold standard method-of-choice for RCTs, is endorsed by CONSORT, respects initial randomization, and provides unbiased estimates of the effect of treatment assignment on outcome measures (Shrier et al., 2014).

In compliance with CONSORT guidelines (Moher, 2010), the analytic plan focused on documenting group × time interactions. Intervention group, and group × time interaction terms were entered as fixed effects, baseline antisocial score as

a covariate, while outcome measures were modeled using maximum-likelihood estimation with a first-order autoregressive covariance structure and with homogeneous variances to account for the correlation between time points. Counts of institutional infractions which had no missing data and had variance greater than the mean were analyzed using negative binomial regression at each time period. Chi-square analyses were conducted on blinding data (perceived group versus actual group). All tests are two-tailed. All analyses were conducted using SPSS (version 23). False discovery rate control (Benjamini & Hochberg, 1995) was employed to control for type I error on the group comparisons within each time period for each instrument, with uncorrected p values reported below in the Results section. Figures are based on estimated marginal means. To assess robustness of any significant findings emerging from the ITT design that used mixed-effects models, sensitivity analyses were run using a per protocol design in which only those completing the intervention were analyzed using repeated measures multivariate analysis of variance (RM-MANOVA).

Results

Participant flow, recruitment, and attrition

Full details on participant flow, including enrollment, group allocation, and follow-up, are given in the Online supplementary material. No participant loss was observed on baseline assessment after randomization. Of the 145 participants, 3.4% were lost to follow-up at either 3, 6, or 12 months (one from omega-3, two from placebo, two from controls—see Online supplementary material for detailed reasons for loss). Groups did not significantly differ in this attrition ($\chi^2 = 0.42$, $df = 2$, $p = 0.81$).

Demographics and adherence to protocol

Demographics. Demographic data are reported in Table 1. No significant group differences were observed on age, ethnicity, violent/non-violent offending, baseline self-report antisocial behavior, baseline officer-report antisocial behavior, and prison infractions, documenting that randomization and stratification procedures were successful.

Adherence to protocol. Average number of drinks taken per week for placebo and omega-3 groups is provided in Table 1. There was no significant group difference in compliance rates ($p = 0.72$).

Blinding success

Groups did not differ in guessing which of the two drink groups they had been allocated to ($p = 0.68$), with 45.7% of the placebo group believing they were assigned to the omega-3 group, compared to 46.8% in the omega-3 group. This indicates that the blinding was successful.

Table 1. Demographics, baseline antisocial behavior, perception of group assignment, and treatment adherence data together with statistical comparisons for intervention groups (standard deviations are in parentheses)

		Controls (n = 51)	Placebo (n = 46)	Omega-3 (n = 48)	Statistic	p value
Age		19.23 (1.31)	19.29 (1.78)	19.22 (1.10)	$F = 0.05$	0.95
Ethnicity	Chinese	35.8%	33.6%	41.7%	$\chi^2 = 4.95$	0.55
	Malay	45.1%	58.7%	47.9%		
	Indian	9.8%	4.3%	2.2%		
	Other	9.8%	2.2%	4.2%		
Violence risk	Low	13.7%	10.9%	10.4%	$\chi^2 = 7.55$	0.48
	Low-moderate	19.6%	37.0%	20.8%		
	Moderate	31.4%	23.9%	37.5%		
	Moderate-high	25.5%	21.7%	16.7%		
	High	9.8%	6.5%	14.6%		
Current conviction	Violent	35.2%	31.7%	33.1%	$\chi^2 = 0.12$	0.91
	Non-violent	64.8%	68.3%	66.9%		
Self-report baseline	Total antisocial	−1.17 (10.54)	0.47 (10.67)	0.80 (8.99)	$F = 0.54$	0.58
	Reactive	−0.43 (6.09)	−0.21 (6.21)	0.67 (5.59)	$F = 0.46$	0.63
	Proactive	−0.22 (4.12)	0.41 (4.05)	−0.16 (3.19)	$F = 0.39$	0.60
	Psychopathy	−0.52 (2.51)	0.28 (2.13)	0.29 (1.91)	$F = 2.22$	0.11
Officer report baseline	Antisocial factor	0.14 (1.03)	0.01 (1.03)	−0.14 (0.92)	$F = 0.45$	0.64
Prison infractions		1.75 (2.48)	1.74 (1.98)	1.88 (2.24)	$F = 0.05$	0.95
Assignment perception	Believe assigned to omega-3	–	45.7%	46.8%	$\chi^2 = 0.77$	0.68
Treatment compliance	Number of juice drinks/week	–	6.14 (1.77)	6.05 (1.30)	$t = 0.26$	0.80

Adverse events

As with the two prior studies of Gesch et al. (2002) and Zaalberg et al. (2010), no adverse events were reported.

Factor analyses of secondary outcome measures

Self-report and officer-report measures of antisocial behavior were factor analyzed separately to provide overarching indicators and to reduce type I error. Analyses produced single overarching measures of both self-report and officer-report antisocial behavior for each of the four time points. In addition, for self-reports only, three factors consisting of reactive-aggressive, proactive-disruptive, and psychopathy were also extracted. Full details are provided in the Online supplementary material.

Self-Reports

Estimated marginal means from mixed-effects analyses for self-report and officer-report measures and prison infractions at all four time points are detailed in Table 2. Analyses below are based on estimated marginal means.

Self-reports. For the general factor of antisocial behavior, the treatment group × time interaction was significant, $F(6,412) = 2.25$, $p = 0.038$. Antisocial scores for all three treatment groups are illustrated in Fig. 1a. At 3 months (end of treatment), the omega-3 group were significantly lower than controls ($p = 0.006$, $d = 0.56$). At 6 months, there was a trend for the omega-3 group to be lower than the placebo group ($p = 0.059$, $d = 0.39$), which was significant at 12 months ($p = 0.045$, $d = 0.43$). No other pairwise comparison was significant. The initial group difference at 3 months survived false discovery rate control.

Analyses were conducted on the three factors to assess specificity of findings. For reactive-aggressive scores, the group × time effect was significant, $F(6,408) = 2.18$, $p = 0.044$ (see Fig. 1b). At 3 months, the omega-3 group was significantly lower than controls ($p = 0.01$, $d = 0.52$). At 6 months, the omega-3 group was significantly lower than the placebo group ($p = 0.009$, $d = 0.54$), and they remained significantly lower at 12 months ($p = 0.013$, $d = 0.51$). No other comparisons were significant. All three comparisons survived false discovery rate control. No group × time interactions were significant for proactive-disruptive ($F = 1.41$, $p = 0.21$) or for psychopathy factors ($F = 1.29$, $p = 0.26$).

Prison officer reports. Group effects are illustrated in Fig. 2. The group × time effect was non-significant, $F(6,367) = 0.92$, $p = 0.48$, although effects were in the same direction as for self-reports. Exploratory post hoc analysis suggested by one reviewer revealed reduced antisocial behavior in the omega-3 group compared to the placebo group at 3 months ($p = 0.019$), 6 months ($p = 0.024$) and also at 12 months ($p = 0.003$).

Prison infractions. Negative binomial regression analyses indicated that group differences were non-significant at all four time points (Wald $\chi^2 = 2.03$, $df = 2$, $p > 0.36$).

Sensitivity analyses

Full details of the per protocol robustness analyses are provided in the online supplement.

Self-reports. Significant group × time interactions and the overall pattern of findings were replicated for the general self-report measure of antisocial behavior ($p = 0.045$) and for the reactive-aggressive factor ($p = 0.049$).

Officer reports. A significant group × time interaction was observed for officer reports ($p = 0.046$). Pairwise comparisons indicated that the omega-3 group were lower than the placebo group at 3 months ($p = 0.019$, $d = 0.52$), 6 months ($p = 0.01$, $d = 0.56$), and 12 months ($p = 0.001$, $d = 0.75$), largely paralleling findings from ITT analyses. Comparisons at all time points survived false discovery rate control.

Officer-reported reactive-impulsive aggression. A proxy measure of officer-reported reactive-impulsive aggression produced a significant group × time interaction ($p =$

Table 2. Unadjusted means with 95% confidence intervals (in parentheses) from mixed-effects models on young offenders' behavioral outcomes in the three intervention groups for the four assessment periods

	Young offender self-report				Officer report	Prison incidents
	Antisocial	Reactive-aggressive	Proactive-disruptive	Psychopathy	Antisocial	
Controls						
0 months	−0.50 (−3.12, 2.12)	−0.16 (−1.61, 1.30)	−0.12 (−1.11, 0.87)	−0.30 (−0.92, 0.33)	−0.02 (−0.20, 0.15)	1.86 (1.06, 2.67)
3 months	2.90 (0.28, 5.52)	1.40 (−0.04, 2.85)	0.89 (−0.10, 1.88)	0.53 (−0.09, 1.15)	−0.06 (−0.24, 0.11)	2.78 (1.98, 3.59)
6 months	0.41 (−2.23, 3.05)	−0.03 (−1.49, 1.43)	0.18 (−0.82, 1.17)	0.22 (−0.41, 0.85)	−0.02 (−0.19, 0.16)	1.33 (0.53, 2.14)
12 months	0.08 (−2.57, 2.72)	0.18 (−1.28, 1.64)	−0.28 (−1.28, 0.71)	0.12 (−0.51, 0.74)	−0.04 (−0.23, 0.15)	2.71 (1.90, 3.51)
Placebo						
0 months	0.20 (−2.56, 2.96)	−0.07 (−1.60, 1.45)	0.21 (−0.83, 1.25)	0.16 (−0.49, 0.81)	0.02 (−0.16, 0.20)	1.74 (0.89, 2.58)
3 months	−0.66 (−3.44, 2.12)	−0.15 (−1.68, 1.39)	−0.15 (−1.20, 0.90)	−0.30 (−0.95, 0.36)	0.12 (−0.07, 0.31)	3.65 (2.81, 4.50)
6 months	1.50 (−1.28, 4.28)	1.40 (−0.14, 2.94)	0.33 (−0.72, 1.38)	−0.14 (−0.80, 0.52)	0.15 (−0.03, 0.34)	1.85 (1.00, 2.69)
12 months	1.93 (−0.88, 4.74)	1.23 (−0.32, 2.79)	0.82 (−0.25, 1.88)	−0.05 (−0.71, 0.61)	0.30 (−0.10, 0.50)	2.80 (1.96, 3.65)
Omega 3						
0 months	0.34 (−2.36, 3.04)	0.27 (−1.23, 1.76)	−0.09 (−1.11, 0.93)	0.17 (−0.47, 0.81)	0.01 (−0.17, 0.18)	1.75 (0.92, 2.58)
3 months	−2.43 (−5.13, 0.27)	−1.35 (−2.84, 0.14)	−0.80 (−1.82, 0.22)	−0.27 (−0.91, 0.37)	−0.10 (−0.29, 0.08)	2.69 (1.86, 3.51)
6 months	−2.23 (−4.94, 0.47)	−1.46 (−2.95, 0.04)	−0.63 (−1.65, 0.39)	−0.14 (−0.78, 0.50)	−0.15 (−0.33, 0.03)	1.48 (0.65, 2.31)
12 months	−2.09 (−4.84, 0.66)	−1.52 (−3.04, −0.00)	−0.51 (−1.55, 0.53)	−0.09 (−0.74, 0.55)	−0.14 (−0.34, 0.07)	2.65 (1.82, 3.47)

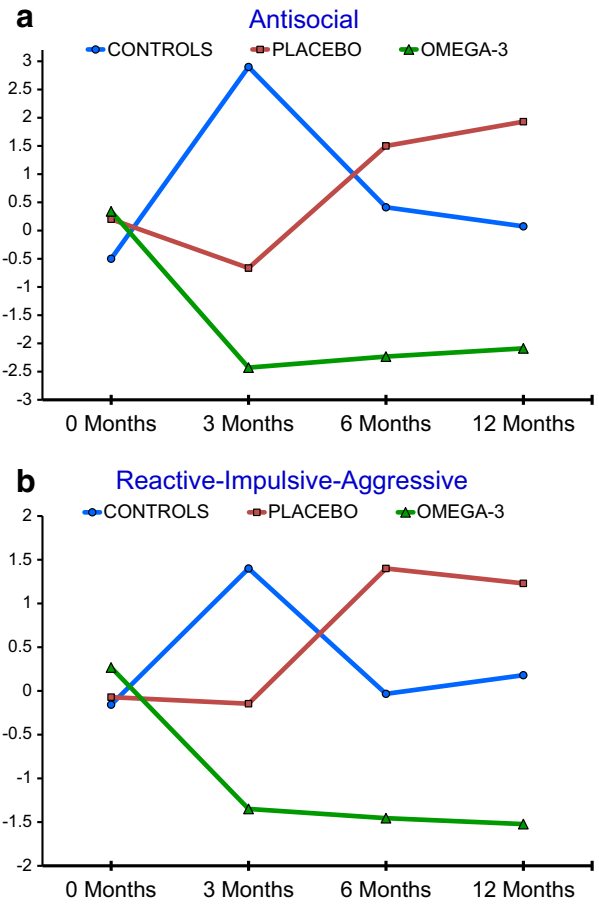

Fig. 1 Illustration of significant group × time interactions showing reductions in the omega-3 groups for (**a**) general self-report antisocial behavior and (**b**) self-report reactive, impulsive, aggressive behavior. For antisocial behavior, the omega-3 group at 3 months was significantly lower than controls ($p < 0.006$), and also lower at 12 months compared to the placebo group ($p = 0.045$). For reactive-impulsive-aggressive behavior, the omega-3 group was significantly lower than controls ($p = .01$) at 3 months, lower than placebo at six months ($p = .009$), and lower than placebo at 12 months ($p = .013$)

0.049) with significant reductions in the omega-3 group compared to the placebo group at 3 months ($p = 0.001$) and 12 months ($p = 0.001$) that withstood false discovery rate control.

Discussion

Main Findings

This study aimed to assess whether omega-3 supplementation could help reduce antisocial and aggressive behavior in young offenders. Partial support was obtained

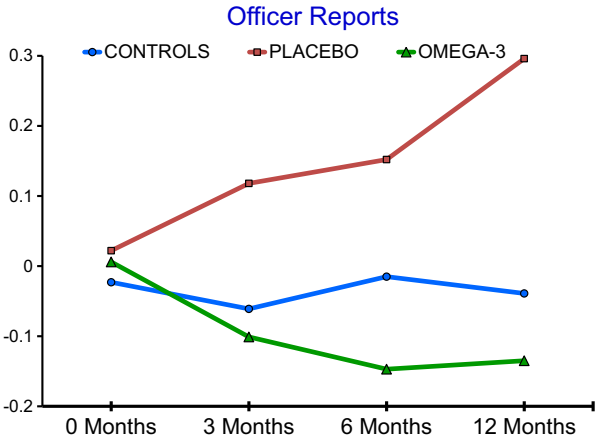

Fig. 2 Illustration of the significant group × time interaction from per-protocol analyses of officer reports of general antisocial behavior showing the decline over time in the omega-3 group. The omega-3 group were lower than the placebo group at 3 months ($p = 0.019$), 6 months ($p = 0.01$), and 12 months ($p = 0.001$)

for supplementation efficacy. Self-reports of overall antisocial behavior were significantly reduced in the omega-3 group both in the short term and the long term. Omega-3 was more effective in reducing reactive, impulsive aggression than proactive aggression or psychopathy both in the short term and the long term. Sensitivity analyses supported the robustness of these self-report findings. While results were non-significant for officer reports based on ITT analyses, post hoc tests nevertheless revealed that the omega-3 groups showed long-term reductions compared to the placebo group at 6 months and 12 months. Sensitivity analyses documented that these significant post hoc officer-report results were buttressed in per-protocol analyses which documented that the omega-3 group evidenced reductions that increased over time in both officer-reported antisocial behavior and also officer-reported reactive-impulsive-aggressive behavior compared to the placebo group, suggesting more robust effects for those completing treatment. No significant reductions in prison infractions were observed. Effect sizes were generally in the low to medium range. Taken together, findings provide partial but not full cross-cultural validation of the two prior prison studies on omega-3 supplementation (Gesch et al., 2001; Zaalberg et al., 2010). It is suggested that further consideration be particularly given to omega-3 supplementation for both offender populations and also non-incarcerated patients presenting with reactive, impulsive forms of aggressive behavior.

More robust effects for reactive, impulsive forms of aggression

The most robust effects were found for reactive, impulsive aggression. Importantly, reductions immediately post-treatment at 3 months were sustained at 6 months and 12 months for self-reports at levels which did not diminish over time, lying in contrast to the proactive aggression/disruptive factor which showed no treatment effects. These findings were replicated with officer reports (see Online supplementary material). This finding is consistent with findings from other studies which have reported that reactive

but not proactive aggression is reduced following omega-3 supplementation (Choy & Raine, 2018; Raine et al., 2016, 2019).

What is the mechanism of action whereby omega-3 particularly reduces impulsive, reactive aggression? One possibility is that omega-3 reduced reactive aggression by enhancing the functioning of the prefrontal cortex. Concentrations of DHA vary throughout the brain and are at their highest in the prefrontal cortex (Laye, Nadjar, Joffre, & Bazinet, 2018), an area critical for impulse control and emotion regulation. Higher levels of omega-3 are associated inter alia with increased functional connectivity in the frontal pole and anterior cingulate, areas that subserve executive functions (Talukdar, Zannroziewicz, Zwilling, & Barbey, 2019). Omega-3 supplementation has also been shown to enhance executive functions (McNamara, Asch, Lindquist, & Krikorian, 2018). Given that reactive-impulsive aggression has been associated with reduced glucose metabolism in the prefrontal cortex, as well as poor executive functions (Thomson & Centifanti, 2018) and also reduced connectivity between the prefrontal cortex and amygdala (Romero-Martinez et al., 2019), prefrontal upregulation is a viable explanation for why omega-3 reduces impulsive-aggressive behavior. Future studies could test this hypothesis by evaluating whether omega-3 supplementation enhances prefrontal functioning as assessed by either neurocognitive or brain imaging measures, and by additionally assessing whether such prefrontal upregulation mediates any effect of omega-3 supplementation in reducing antisocial behavior.

Partial support for omega-3 efficacy

Findings can only be considered partial support for the notion that omega-3 may have efficacy in reducing general forms of antisocial behavior as no group × time interaction was observed for officer reports using an ITT design incorporating all participants, although post hoc analyses did document significant improvement in the omega-3 group. This caveat must in turn be tempered by three considerations. First, per-protocol analyses of officer reports based on those completing treatment *did* show a significant group × time interaction, with the omega-3 group compared to the placebo group showing reductions in antisocial behavior post-treatment which increased in size as time progressed. As significant per-protocol effects were also observed for self-reports, important cross-informant corroboration was observed for those completing treatment. Second, officer reports were non-significantly *negatively* correlated with self-reports ($r = -0.08$, $p = 0.33$) indicating that they reflect a different form of antisocial behavior. They also failed to yield separable sub-factors that would be expected and which were obtained from self-reports. Third, a prior RCT of omega-3 supplementation on offenders also failed to observe significant effects on all four prison officer measures in the face of trends for self-reported improvement (Zaalberg et al., 2010). These three considerations caution against dismissal of positive findings that emerged and call for future multi-informant research that can resolve these oppositional findings.

A further caveat is the null findings for prison infractions. In contrast, the two prior omega-3 RCTs on offender populations both obtained significant effects for institutional disciplinary records (Gesch et al., 2002; Zaalberg et al., 2010). This discrepancy could be due to the highly skewed distribution of institutional offending in Singapore and relative rarity of serious institutional offending in Singapore compared to Western countries, including the absence of drug and alcohol offenses that have been significant

in other prison studies (Zaalberg et al., 2010). Furthermore, prison infractions were uncorrelated with both officer reports ($r = 0.08$) and self-reports ($r = 0.12$) of antisocial behavior, again indicating the different nature of this prison infraction measure. Recognition of these null findings must be balanced with the significant self-reports and significant officer reports from per-protocol analyses that overall render findings as giving some partial support for the two prior prison studies.

One reason why only partial support was obtained for omega-3 efficacy in reducing antisocial behavior concerns geography. Southeast Asia has the highest omega-3 intake in the world (Micha et al., 2014; Food and Agriculture Organization of the United Nations, 2013), with substantial increases occurring in both seafood and plant omega-3 from 1990 to 2010 (Micha et al. 2014), a time period during which participants in the current study were growing up. Singaporeans have been reported to consume more than five times the seafood intake of those in the United States (United States Department of Agriculture, 2017). Cross-national research has documented a relatively strong negative correlation ($r = -0.68$) between seafood consumption throughout the world and homicide rates, with high seafood consumption associated with low homicide rates (Hibbeln, 2001). Conceivably therefore, there may be a ceiling effect in Singapore of overall higher baseline seafood consumption that limits the impact of omega-3 in enhancing neurobiological functioning and reducing antisocial behavior. This may have detracted from the ability to detect effects with omega-3 supplementation, particularly compared to the two prior studies in England and the Netherlands where omega-3 intake is comparatively lower (Micha et al., 2014). Future research could test whether effect sizes in treatment studies are somewhat larger in countries with less seafood intake than in Singapore.

Limitations

Limitations need to be acknowledged. The sample size of 145 is not large, with approximately 48 in each group. While this limits power to detect significant effects, it is twice as large as the median sample size ($N = 22$) calculated from prior omega-3 studies of antisocial behavior (24). Second, while the supplementation period of 3 months is normative for omega-3 studies, longer treatment duration could be more efficacious. Third, while contrasting results as a function of reporter are relatively common in the field (De Los Reyes, Thomas, Goodman, & Kundey, 2013), they underline the need for replication and generalization. Fourth, effect sizes generally were not large, ranging from small to medium, although this is consistent with meta-analytic findings on aggression (Gajos & Beaver, 2016). Fifth, we caution that per-protocol analyses entail missing data that should be treated cautiously compared with ITT analyses which include all participants. These limitations in turn need to be balanced with relative strengths which include the rigorous randomized, stratified, double-blind, placebo-controlled, parallel-group design, the use of multiple report sources that include sub-forms of antisocial behavior, two control groups, low attrition, successful blinding, robustness checks, consistent supplementation for 3 months, and longer-term follow-up 9 months after treatment termination which is rare in this field.

Conclusions

In conclusion, partial support was observed for the efficacy of omega-3 supplementation in reducing antisocial behavior in young offenders, particularly with respect to more reactive, impulsive aggressive behavior. The potential implication of these findings for criminology, psychiatry, and clinical psychology lies in the future potential for a benign neurobiological intervention to reduce antisocial and aggressive behavior in offenders, a treatment approach which is currently not operationalized in prison settings. Given reports of the efficacy of omega-3 supplementation in reducing aggression, anger control, and behavior problems in psychiatric disorders that include borderline personality (Bozzatello, Rocca, & Bellino, 2018), substance abuse (Buydens-Branch & Branchey, 2008), and youth with depression (Young, Arnold, Wolfson, & Fristad, 2017), and given evidence for its efficacy in treating mental disorders (Firth et al., 2019), omega-3 could be particularly effective in reducing antisocial and aggressive behavior in offenders who also present with mental illness.

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