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Reduction in behavior problems with omega-3 supplementation in children aged 8–16 years: a randomized, double-blind, placebo-controlled, stratified, parallel-group trial

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Background: While limited evidence suggests that omega-3 supplementation may reduce antisocial behavior in children, studies have not reported on posttreatment follow-up and most treatment periods have been of short duration. This study tests the hypothesis that omega-3 supplementation over 6 months will reduce behavior problems in children both at the end of treatment and at 6 months post treatment. **Methods:** In this randomized, double-blind, placebo-controlled, stratified, parallel-group trial, a community sample of 8–16 year old children were randomized into a treatment group ($N = 100$) and a placebo-control group ($N = 100$). The 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. Participants, caregivers, and research assistants were blinded to group assignment. The primary outcome measures of externalizing and internalizing behavior problems were reported by both caregivers and their children in a laboratory setting at 0 months (baseline), 6 months (end of treatment) and 12 months (6 months post treatment), together with the secondary outcome measures of parental antisocial behavior. Data were analyzed on an intention-to-treat basis including all participants. Trial registration: ClinicalTrials.gov: http://clinicaltrials.gov/ct2/show/NCT02016079?term=mauritius&rank=2. **Results:** Significant group × time interactions were observed with the treatment group showing long-term improvements in child behavior problems. The average posttreatment effect size was $d = -.59$. Effects were documented for parent reports, but with the exception of proactive and reactive aggression, child-report data were nonsignificant. Parents whose children took omega-3 showed significant posttreatment reductions in their own antisocial and aggressive behavior. This improvement in caregiver behavior partly mediated the improvements observed in child behavior. **Conclusions:** Findings provide initial evidence that omega-3 supplementation can produce sustained reductions in externalizing and internalizing behavior problems. Results are the first to report improvements in caregiver behavior, and to establish this improvement as a part-mechanism for the efficacy of omega-3. **Keywords:** Omega-3, externalizing, internalizing, aggression, randomized trial.

Introduction

Poor nutritional status during pregnancy has been found to predispose to antisocial personality disorder in adulthood (Neugebauer, Hoek, & Susser, 1999), while poor nutrition in early childhood is associated with increased aggressive and conduct-disordered behavior in childhood and adolescence (Liu, Raine, Venables, Dalais, & Mednick, 2004). Poor nutrition is hypothesized to negatively impact brain structure and function which in turn predisposes to risk factors for antisocial behavior (Liu, 2011; Raine, 2008). Brain abnormalities have been found to characterize not just adult offenders (Glenn & Raine, 2014), but also conduct disordered children and children with callous-unemotional traits (Fairchild et al., 2011; Viding et al., 2012). As such, poor nutrition is a plausible risk factor for the development of antisocial and aggressive behavior.

Given this nutrition – brain – antisocial behavior linkage, improving nutrition may help improve child behavior problems. Vitamin and mineral supplementation may reduce antisocial behavior, although evidence here is relatively sparse (Benton, 2007). Tryptophan supplementation (an essential amino acid) reduces aggression and increases agreeableness in some studies (Young, 2013). Another nutritional component coming under increasing scrutiny is omega-3. Fish consumption across the world is negatively correlated with cross-country homicide rates (Hibbeln, 2001). Two randomized controlled trials (RCTs) have shown that omega-3 supplementation reduces antisocial behavior in young prisoners in both England (35% reduction) and the Netherlands (34% reduction) (Gesch, Hammond, Hampson, Eves, & Crowder, 2002; Zaalberg, Nijman, Bulten, Stroosma, & van der Staak, 2010), and reduces aggression in male adult men without a

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history of aggression (Long & Benton, 2013). Findings from RCTs in children and adolescents are mixed, with some finding limited evidence for efficacy (Gustafsson et al., 2010) while others do not (Milte et al., 2012). The latter study had 52% power to detect a significant effect, and consequently null results may be partly due to lack of adequate power.

Several factors may contribute to conflicting findings. Dosages of omega-3 have varied across studies and are generally relatively low – with some as low as 124 mg of omega-3/day (Gesch et al., 2002). Second, treatment length has been relatively short, with some as short as 1 month with a median of approximately 3 months (Sinn, Milte, & Howe, 2010). Third, because there appears to be no comprehensive meta-analysis of omega-3 supplementation on child antisocial behavior, there is a clear need for further RCTs on this behavior problem. Fourth, sample sizes are relatively small not just in studies on antisocial behavior, but also in clinical trials in general, with 50% having fewer than 70 participants (Califf et al., 2012).

There are also methodological limitations in prior studies. Some are correlational, yet RCTs are the building blocks of evidence-based practice (Maughan, 2013) and are critical for parsing causality. Second, no study on behavior problems has followed up children post treatment to assess for long-term efficacy. Third, studies have not examined changes in caregiver behavior; improvements in the child's behavior could plausibly improve the behavior of the parent, and this could further contribute to a delayed long-term improvement in child behavior. Fourth, it is unclear whether findings from the clinic and correctional settings generalize to the community. Fifth, while children with callous-unemotional traits have relatively poor treatment outcome (Frick, Ray, Thornton, & Kahn, 2014), we know of no attempts to reduce such traits using nutritional intervention.

To help address these issues, this study's primary aim was to test whether omega-3 supplementation reduces child and adolescent antisocial/aggressive behavior. The main hypothesis was that omega-3 supplementation will reduce externalizing behavior problems both at the end of treatment and also 6-months post treatment. Secondary aims were to assess for reduction in internalizing behavior problems, and to examine any influence of nutritional supplementation to the child on their caregiver's antisocial behavior, and whether any such parental change could contribute to child behavior change.

Methods

Trial design

The design consisted of a randomized, double-blind, placebo-controlled, stratified, parallel-group trial (1:1 ratio) of children in the community. Trial design remained unchanged throughout the study.

Study setting

The study took place in interview rooms at the Joint Child Health Project headquarters in Quatre Bornes, Mauritius, from November 2009 to December 2011. Further details of this country and past research can be found in Raine, Liu, Venables, Mednick, and Dalais (2010). The study was registered in ClinicalTrials.gov under the title 'Effect of Omega-3 Supplementation on Child Behavior Problems' at http://clinicaltrials.gov/ct2/show/NCT02016079?term=mauritius&rank=2.

Participants

Participants consisted of 200 children of parents who themselves had participated in the Mauritius Child Health Project (Raine et al., 2010). Children had to be aged between 8 and 16 years old, willing to participate in an RCT, and residing in the community. Exclusion criteria consisted of: (a) allergy to fish or fish products, (b) use of fish-oil supplementation in the past 6 months, (c) intellectual disability. Written informed consent was obtained from the parents, while assent was obtained from the child. During consenting, participants were informed of the study hypothesis that omega-3 may help improve child behavior. Ethical approval was obtained from IRB boards in Mauritius (Ministry of Health) and the US (University of Pennsylvania).

Reviews of RCTs have commented that median sample sizes in RCTs are relatively modest, with estimates of 46, 54, 65, and 80 from different reviews (Moher, 2010), and which also characterize omega-3 RCTs of psychopathology (Sinn et al., 2010). We consequently aimed for a somewhat larger study to detect a small-to-medium effect size. Our sample size of 200 had power to detect an effect size of $d = .35$ with power of .80, $\alpha = .05$, one-tailed.

Omega-3 intervention

Omega-3 supplementation. This consisted of a 200 ml drink (Smartfish Recharge). The base drink in both treatment and control conditions consisted of fruit juice from apple, pear, pomegranate, aronia, and passion fruit. It also contained vitamin D (0.85 μg) and antioxidants (ferric reducing ability of plasma value of 0.71 mmol/100 g). For the treatment condition only, a total of 1000 mg of omega-3 (300 mg of DHA, 200 mg of EPA, 400 mg of alpha-linolenic acid, and 100 mg of DPA) was added to the base drink. Placebo drinks were matched exactly with the fish-oil drink in terms of size, appearance, and flavor.

This drink was chosen because: (a) it contains an appreciably higher dosage of omega-3 than standard capsules in a relatively small liquid quantity (60.6% of the size of a standard can of cola) suitable for child consumption, (b) the fruit-flavored drink may be better tolerated and result in higher compliance with children than standard capsules.

Treatment duration and administration. Treatment duration was 6 months. This duration was chosen because prior treatment studies have usually been 2–4 months (Sinn et al., 2010), and a somewhat longer treatment period may be more effective in producing longer-term brain and behavioral change. The omega-3 drink was administered by the parents to their children each day at a suitable time.

Outcome measures

The predefined primary outcome measures were externalizing behavior problems including aggressive behavior. Secondary outcomes included internalizing behavior problems and parental aggressive and psychopathic behavior.

Child behavior checklist (CBCL) and youth self report (YSR). The CBCL (parent report) and YSR (child report) are well-standardized, extensively used psychometric instruments with high reliability/validity in many countries (Achenbach & Rescorla, 2001). Measurement invariance of the CBCL has also been documented on this cohort in Mauritius (Yarnell et al., 2013). The CBCL/YSR contains two empirically derived broadband scales (externalizing/internalizing) and eight syndrome scales. Externalizing behavior consists of Aggressive Behavior and Rule-Breaking Behavior scales, while the internalizing behavior domain consisted of Anxious/Depressed, Withdrawn/Depressed, and Somatic Complaints scales. Additional syndrome scales include Attention Problems, Social Problems, Thought, and Other Problems.

Reactive-proactive aggression questionnaire (RPQ). Children completed this self-report instrument which yields scales of reactive, proactive, and total aggression (Raine et al., 2006). Reliability and validity have been documented in Baker, Raine, Liu, and Jacobson (2008), Fossati et al. (2009), and Fung, Raine, and Gao (2009).

The antisocial personality screening device (APSD). This 20-item scale assesses parent-reported child and adolescent psychopathic traits (Frick, Bodin, & Barry, 2000). It consists of three subscales to assess callous-unemotional traits, narcissism, and impulsivity.

Psychopathic personality inventory (PPI). Parents completed the short version of the self-report Psychopathic Personality Inventory (PPI – Lilienfeld & Andrews, 1996). It yields a global psychopathy score, and eight subscales measuring social potency, cold-heartedness, fearlessness, impulsive nonconformity, stress immunity, Machiavellian egocentricity, blame externalization, and carefree nonplanfulness. The PPI was designed for use in nonclinical settings and has been shown to be reliable and valid in community samples (Lilienfeld & Andrews, 1996).

Randomization and stratification

After giving informed consent, participants were randomized into treatment and placebo groups with blocking on a 1:1 ratio (Suresh, 2011). Prior to initial group assignment, matched pairs of participants were created from the computer data--base, with matching on age band (8–10, 11–13, 14–16), gender (male/female), and ethnicity (Indian/Creole). This stratification procedure aims to balance groups on key demographic variables. Within each of the 100 pairs, restricted randomization to group was conducted using a computer-generated list of random numbers generated by SPSS.

Adherence to protocol

Adherence to the treatment regimen was assessed at the end of treatment by asking caregivers how often the drink had been consumed (number of drinks/week). Adherence was also assessed by assays of omega-6 and omega-3 from finger-prick blood taken at baseline and 6 months (end of treatment). For detailed methods see Lin, Loewke, Hyun, Leazer, and Hibbeln (2012).

Statistical methods

An intention-to-treat (ITT) design using all randomly assigned participants (200) was employed for all data analyses. Data missing due to loss at follow-up were imputed using the last observation carried forward strategy (White, Horton, & Pocock, 2011). The ITT approach is considered a gold standard 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) as well as a more realistic estimate of treatment effects in the real world where people drop out of treatment (Del Re, Maisel, Blodgett, & Finney, 2013).

Analyses focused on documenting group × time interactions, with effect sizes calculated using partial η^2. Differences in baseline scores were compared using two-tailed independent *t*-test. Where differences were observed (only for child self-report RPQ), baseline scores were entered as covariates to equalize groups at baseline.

To assess whether any improvement in parental behavior may partly account for the treatment effect on child behavior, mediation analyses were performed using the PROCESS SPSS macro (Hayes, 2013). To test significance of the indirect effects (i.e. mediation), bias-corrected confidence intervals for the indirect effects were generated using 10,000 bootstrap samples. Bootstrapping was used because it constitutes a nonparametric resampling procedure that makes more realistic assumptions on the sampling distribution of the indirect effect (MacKinnon, Lockwood, & Williams, 2004). To assess extent of mediation, the reduction in variance explained in treatment outcome by the intervention after controlling for improved parental behavior (the mediator) was calculated in a two-step regression. All analyses were conducted using SPSS (version 20; IBM, Amonk, NY, USA) .

Results

Participant flow and recruitment

Participant flow and recruitment details are outlined in the Supplemental Table S1. No participant loss was observed on baseline assessment after randomization. Of the 200 participants, 16 (8%) were lost to follow-up at either 6 or 12 months (5 from omega-3, 11 from placebo – see Table S1 for details of reasons for loss). Groups did not significantly differ in this attrition ($\chi^2 = 2.51$, $df = 1$, $p = .11$).

Demographics and adherence to protocol

Demographics. Demographic data are reported in Table 1. No significant group differences were observed, documenting that stratification procedures were successful.

Adherence to protocol. Average number of drinks taken per week for each group are provided in Table 1. There was no significant group difference in compliance rates ($p = .73$).

Adherence to the protocol was also assessed using blood omega-3 fatty acid levels (see Table 1). A significant group × time interaction indicated that groups did not differ at baseline, but post treatment (6 months), the omega-3 group had significantly higher omega-3 levels than controls ($p < .001$), indicating *increased* omega-3 levels over treatment.

Child behavioral problems

Means and *SD*s on parent and child outcome measures for children at all three time points,

group × trial interactions, effect sizes for interactions and posttreatment group differences are detailed in Table 2.

Parent report. Significant group × time interactions were observed for all internalizing and externalizing subscales, except for somatic complaints. A significant interaction was also obtained for callous-unemotional traits. All other results were nonsignificant. Interactions for externalizing, internalizing, and callous-unemotional behavior are illustrated in Figure 1. The effect size for group differences at 12 months for all CBCL behavior problem scales was $d = -.59$ (95% C.I. = −.84 to −.35).

Child report. In contrast to parent reports, for most self-report measures no group × trial interactions were observed. Significant interactions were, however, observed for self-report reactive ($p < .0001$) and proactive ($p = .02$) aggression, as well as total aggression ($p < .0001$). Both forms of aggression showed significant intervention declines only in the omega-3 group by the end of treatment at 6 months (average $d = -.80$, 95% C.I. = −1.08 to −.52) (see Figure S1).

Parental antisocial behavior

Means, *SD*s, group × time interactions, and posttreatment effect sizes are shown in Table 3. Significant group × time interactions were observed for total PPI scores, six of the eight PPI subscales, and reactive (but not proactive) aggression. As indicated in Figure 2, total psychopathy scores declined at 6 months in both groups during treatment, but while scores for placebo parents returned to baseline at follow-up, the reduction in parents of the omega-3 group was maintained 6 months post treatment at the 12 month time-point.

For reactive aggression, all groups showed declines over time, but the within-group posttreatment decline was greater in the omega-3 group than in controls with respect to both 6-12 months within-group change scores ($t = 2.15$, $df = 198$, $p = .04$, $d = -.30$, CI = −.03 to −.58) and also 0–12 month change scores ($t = 2.12$, $df = 198$, $p = .04$, $d = -.30$, CI = −.02 to −.58). Groups did not differ from each other at the end point (12 months).

Table 1 Demographic and adherence data together with statistical comparisons for placebo and omega-3 groups

	Placebo	Omega-3	Statistic	*p*
Demographics				
Age (*SD*)	11.57 (2.12)	11.07 (2.21)	$t = 1.62$	.11
IQ (*SD*)	99.94 (13.52)	101.23 (14.54)	$t = 0.65$	.52
Sex				
Female (*N*)	48	48	$\chi^2 = 0.0$	1.0
Male (*N*)	52	52		
Ethnicity				
Indian (*N*)	59	57	$\chi^2 = 0.08$	.77
Creole (*N*)	41	43		
Religion				
Hindu (*N*)	28	28	$\chi^2 = 0.11$	.95
Muslim (*N*)	32	30		
Catholic (*N*)	40	42		
Adherence				
N Drinks/ week	6.49 (1.04)	6.54 (0.88)	$t = 0.34$	.73
Omega-3 blood level:				
Before	21.49 (7.44)	22.73 (7.55)	$t = 1.16$	.25
After	22.29 (7.12)	26.39 (9.33)	$t = 3.49$	.001

Influence of placebo effects

Because the above results documented a short-term placebo effect for parent reports of child behavior, groups were examined for differences in their belief in group assignment, and whether this could explain group differences in child behavior. By the end of treatment at 6 months, caregivers with children randomized into the treatment group were more likely to believe their children were receiving omega-3 (97%) compared to the placebo group (53%) ($\chi^2 = 51.63$, $df = 1$, $p < .0001$, $\eta = .51$).

To assess if this belief influenced parental perception of their child's behavior, this measure was entered as a covariate in all previously significant analyses. After controlling for parental belief in treatment allocation, the group × time interaction for parental reports remained significant for externalizing behavior ($F[2,394] = 7.59$, $p = .001$, $\eta^2 = .04$) and internalizing behavior ($F[2,394] = 6.44$, $p = .002$, $\eta^2 = .03$). All other previously significant findings remained significant ($p < .05$). One previously nonsignificant interaction for narcissism became significant after controlling for parental belief ($F[2,195] = 8.44$, $p = .048$, $\eta^2 = .02$).

Factors influencing improvement in parental behavior

We tested whether improvements in the child's behavior at 12 months partly accounted for improvement in their parent's behavior at 12 months. Improvement in child callous-unemotional traits (indirect effect: $\beta = .04$, $p < .05$), reactive aggression (indirect effect: $\beta = .02$, $p < .05$), and total RPQ aggression (indirect effect: $\beta = .02$, $p < .05$) all separately mediated improvement in parental psychopathy, but not parental reactive aggression. No other child improvements were found to mediate improved parental behavior ($p > .05$). In total, improvement in child behavior following treatment accounted for 38.7% of the improvement in parental antisocial behavior.

Table 2 Means and standard deviations for child behavior outcome measures in placebo and omega-3 groups for the three assessment periods, together with statistical comparisons and effect sizes

	Placebo mean 0 months (*SD*)	Omega-3 mean 0 months (*SD*)	Placebo mean 6 months (*SD*)	Omega-3 mean 6 months (*SD*)	Placebo mean 12 months (*SD*)	Omega-3 mean 12 months (*SD*)	Effect size for mean group difference at 12 months, Cohen's *d* (95% C.I.)	Main group effect, *F* (*df* = 1)	Group × time interaction, *F* (*df* = 2)	Effect size for group × time interaction, partial η^2
Parent report										
Child behavior checklist										
CBC externalizing	8.78 (8.44)	8.33 (9.01)	6.97 (8.79)[a]	7.79 (8.17)[a]	7.79 (8.95)	5.05 (6.75)	−.35 (−.62, −.07)	.54	8.74**	.04
CBC internalizing	8.88 (8.48)	7.45 (7.84)	5.22 (6.22)[a]	4.94 (5.90)[a]	6.72 (7.88)[b]	3.14 (4.76)[b]	−.55 (−.83, −.27)	4.59*	6.33**	.03
CBC rule-breaking	1.58 (1.97)	1.32 (2.27)	1.29 (2.24)[a]	1.36 (1.77)	1.71 (2.41)[b]	.64 (1.67)[b]	−.52 (−.80, −.23)	2.73	10.85**	.05
CBC aggression	7.20 (6.93)	7.01 (7.07)	5.68 (6.90)[a]	6.43 (6.82)	6.08 (6.96)	4.41 (5.45)[b]	−.33 (−.71, −.05)	.19	6.18**	.03
CBC attention problems	3.54 (3.72)	3.53 (3.29)	2.29 (3.00)[a]	2.64 (2.95)[a]	3.13 (3.09)[b]	1.57 (1.93)[b]	−.61 (−.90, −.32)	1.29	12.01**	.06
CBC withdrawn	3.00 (2.84)	2.28 (2.71)	1.54 (1.96)[a]	1.54 (2.07)[a]	2.40 (2.70)[b]	1.01 (1.67)[b]	−.62 (−.90, −.34)	6.74*	8.37**	.04
CBC somatic	2.09 (2.69)	1.60 (2.14)	1.52 (2.34)[a]	1.15 (2.00)	1.07 (1.87)	.69 (1.43)[b]	−.23 (−.51, .05)	3.05	.09	.00
CBC anxious/depressed	3.97 (4.41)	3.66 (4.47)	2.27 (3.03)[a]	2.30 (3.22)[a]	3.26 (4.26)[b]	1.44 (2.68)[b]	−.51 (−.79, −.23)	2.58	7.10**	.04
CBC social problems	2.06 (2.41)	1.80 (2.00)	1.13 (1.79)[a]	1.23 (1.63)[a]	1.84 (2.11)[b]	.77 (1.34)[b]	−.61 (−.89, −.32)	3.78	8.37**	.04
CBC thought problems	.69 (1.22)	.75 (1.32)	.44 (1.02)	.36 (.80)[a]	.64 (1.26)	.13 (.51)[b]	−.53 (−.81, −.25)	2.46	6.01**	.03
CBC other problems	5.13 (4.67)	4.23 (4.35)	3.35 (3.82)[a]	3.30 (3.56)[a]	4.02 (4.66)	2.29 (2.62)	−.46 (−.74, −.18)	3.41	5.37**	.03
Antisocial process screening device										
APSD callous-unemotional	4.60 (2.25)	4.68 (2.22)	3.06 (2.32)[a]	3.55 (2.32)[a]	3.96 (2.39)[b]	2.58 (2.37)[b]	−.58 (−.86, −.30)	1.22	13.69**	.07
APSD narcissism	2.44 (2.84)	2.70 (2.62)	3.03 (3.36)[a]	2.76 (3.12)	2.39 (2.91)[b]	2.38 (2.86)	−.00 (−.28, .28)	.00	1.05	.01
APSD impulsivity	2.68 (2.16)	2.37 (1.98)	2.98 (2.61)	2.57 (2.27)	2.24 (2.29)[b]	1.99 (2.33)[b]	−.11 (−.39, .17)	1.35	.16	.00
APSD total	9.83 (5.53)	9.75 (5.08)	9.07 (7.04)	8.88 (6.17)	8.59 (6.14)	6.95 (5.75)[b]	−.28 (−.55, .00)	.74	2.97	.02
Child report										
Youth self report										
YSR externalizing	8.81 (7.23)	11.47 (6.49)	7.59 (7.10)[a]	10.17 (6.68)[a]	7.60 (7.77)	9.82 (6.87)	.30 (.02, .58)	.54	.34	.00
YSR internalizing	13.70 (11.05)	13.80 (10.45)	12.38 (11.77)	14.33 (11.37)	10.62 (9.08)[b]	13.27 (12.30)	.25 (−.03, .52)	3.94*	2.30	.01
YSR rule-breaking	1.64 (1.97)	2.65 (2.02)	1.64 (2.01)	1.89 (2.02)[a]	1.63 (1.93)	2.05 (2.12)	.21 (−.07, .49)	1.39	1.24	.01
YSR aggression	7.17 (5.76)	8.82 (5.19)	5.95 (5.65)[a]	8.28 (5.26)	5.97 (6.31)	7.77 (5.54)	.30 (.02, .58)	7.29**	.68	.00
YSR attention problems	3.38 (3.07)	4.38 (2.61)	2.91 (2.93)	3.81 (2.74)[a]	2.58 (2.83)	3.77 (3.26)	.39 (.11, .67)	2.30	1.48	.01
YSR withdrawn	2.60 (2.19)	2.73 (2.10)	2.54 (2.46)	2.41 (1.97)	2.06 (1.90)[b]	2.46 (2.18)	.20 (−.08, .47)	.12	1.97	.01

Table 2 (continued)

	Placebo mean 0 months (*SD*)	Omega-3 mean 0 months (*SD*)	Placebo mean 6 months (*SD*)	Omega-3 mean 6 months (*SD*)	Placebo mean 12 months (*SD*)	Omega-3 mean 12 months (*SD*)	Effect size for mean group difference at 12 months, Cohen's *d* (95% C.I.)	Main group effect, F (df = 1)	Group × time interaction, F (df = 2)	Effect size for group × time interaction, partial η^2
YSR somatic	1.16 (1.33)	1.25 (1.75)	.90 (1.31)	1.26 (1.56)	.98 (1.59)	1.18 (1.67)	.12 (−.15, .40)	2.20	1.24	.01
YSR anxious/ depressed	4.97 (4.49)	4.91 (4.05)	4.47 (4.48)	5.33 (4.65)	3.79 (3.51)[b]	4.80 (4.93)	.24 (−.04, .51)	4.40*	2.48	.01
YSR social problems	3.32 (2.42)	3.09 (2.03)	2.86 (2.32)[a]	3.62 (2.52)	2.30 (1.97)[b]	3.07 (2.28)[b]	.36 (.08, .64)	11.79**	5.55**	.03
YSR thought problems	1.47 (2.14)	1.25 (1.56)	1.47 (1.91)	1.71 (2.07)[a]	1.52 (1.89)	1.82 (2.18)	.15 (−.13, .42)	3.64	1.77	.01
YSR other problems	7.17 (5.76)	8.82 (5.19)	5.44 (4.72)[a]	5.98 (3.16)[a]	5.15 (3.93)	6.48 (3.94)	.33 (.06, .62)	5.03*	1.59	.01
Reactive proactive aggression questionnaire										
RPQ proactive aggression	.67 (1.28)	1.52 (2.12)	.96 (2.09)	.67 (1.30)[a]	.83 (2.03)	1.27 (2.37)[b]	.20 (−.08, .48)	2.81	4.02*	.02
RPQ reactive aggression	3.91 (3.85)	6.05 (3.40)	4.61 (4.34)	3.96 (3.02)[a]	4.17 (4.14)	5.13 (3.35)[b]	.25 (−.02, .53)	4.58*	7.88**	.04
RPQ total aggression	4.58 (4.67)	7.57 (4.95)	5.57 (5.99)	4.63 (3.87)[a]	5.00 (5.72)	6.40 (5.16)[b]	.26 (−.02, .54)	5.76*	8.58**	.04

[a]Indicates statistically significant ($p < .05$) within group behavior change from 0 to 6 months.
[b]Indicates statistically significant ($p < .05$) within group behavior change from 6 to 12 months.
*$p < .05$; **$p < .01$,

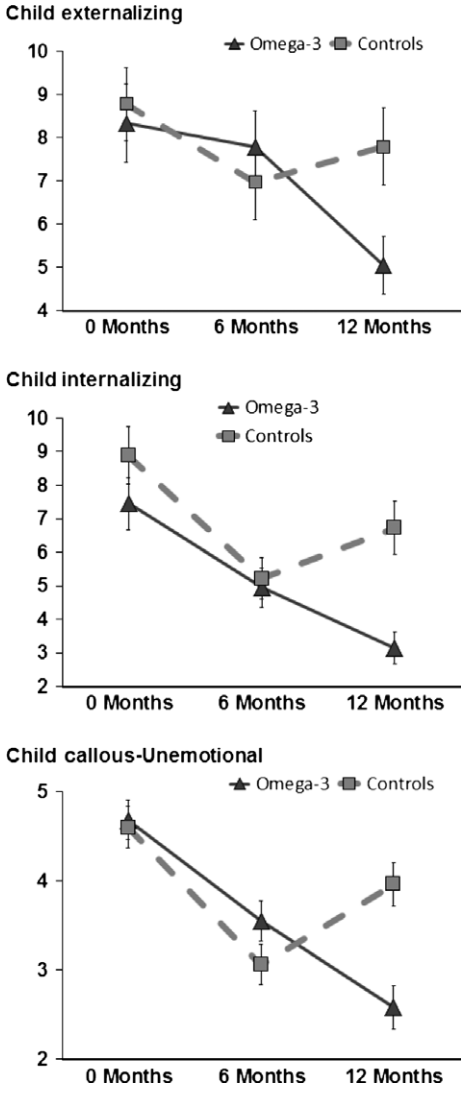

Figure 1 Significant group × time interactions (with standard error bars) for parents' reports of child externalizing behavior, child internalizing behavior, and child callous-unemotional traits

Factors accounting for improvement in child behavior

Omega-3 treatment of the child was associated with improvements in their parent's behavior. Improved parental behavior may therefore partly account for the treatment effect on child behavior.

Testing this hypothesis, changes in parental psychopathy partly mediated child treatment outcomes for callous-unemotional traits (indirect effect: $\beta = .06$, $p < .05$), reactive aggression (indirect effect: $\beta = .06$, $p < .05$), and total RPQ aggression (indirect effect: $\beta = .06$, $p < .05$). Changes in parental reactive aggression partly mediated child treatment effects for anxious-depressed (indirect effect: $\beta = .02$, $p < .05$). No other parental improvement mediated improved child behavior ($p > .05$). In total, improvement in parental behavior accounted for 60.9% of the improvement in child antisocial behavior and 40.0% of the improvement in child anxious-depressed behavior.

Adverse events

No major adverse events were reported. Minor adverse events during the 6 month treatment period were reported by 17 parents (8.5%) and 6 children (3%) (see Table S2). There were no significant group differences for parent reports ($\chi^2 = 1.61$, $df = 1$, $p = .21$) or child reports ($\chi^2 = 0.69$, $df = 1$, $p = .41$). No participant withdrew due to these minor events.

Discussion

The study's main finding was that omega-3 supplementation for 6 months resulted in a 41.6% reduction in parent-rated child externalizing behavior half-a--year after treatment ended. A similar long-term reduction (68.4%) was observed for internalizing behavior. Results could not easily be attributed to placebo expectations. Findings are mitigated by the failure to observe similar effects for child self-reports, with the exception of significant short-term reductions in self-report child reactive (58.9% reduction) and proactive (49.7%) aggression. In the parents of treated children, significant reductions were also observed in parental psychopathy and reactive aggression. Improvement in parental behavior accounted for 60.9% of the improvement in child antisocial behavior. To our knowledge, this is the first study to document support for the longer-term posttreatment efficacy of omega-3 in reducing child and adolescent externalizing and internalizing behavior, and to document reduced antisocial behavior in caregivers.

Improvements in child behavior problems

In addition to significant improvements in aggressive and antisocial behaviors, the medium effect size ($d = -.58$) for long-term improvement in callous-unemotional traits is notable given the recent addition of this trait as a specifier in DSM-V (American Psychiatry Association, 2013) and the increasing interest in child psychopathic-like behavior (Frick et al., 2014). This finding might be expected as low omega-3 has been associated with high callous-unemotional traits in children with ADHD (Gow et al., 2013). In contrast, 18 out of 20 treatment studies report poorer outcomes in antisocial adolescents with callous-unemotional traits compared to those without these traits (Frick et al., 2014). Furthermore, there is very little research focused on callous-unemotional traits themselves (Frick et al., 2014). In this context, omega-3 interventions may be an option in tackling this particular treatment challenge.

While the primary focus of this study was on antisocial and aggressive behavior, positive treatment effects were also observed for almost all internalizing behavior problems. While omega-3 supplementation has been shown in some studies to reduce childhood depression (Nemets, Nemets, Apter, Bracha, & Bel-

Table 3 Means and standard deviations (in parentheses) for parent self report on outcome measures in placebo and omega-3 groups for the three time periods, together with statistical comparisons and effect sizes

	Placebo mean 0 months (*SD*)	Omega-3 mean 0 months (*SD*)	Placebo mean 6 months (*SD*)	Omega-3 mean 6 months (*SD*)	Placebo mean 12 months (*SD*)	Omega-3 mean 12 months (*SD*)	Effect size for mean group difference at 12 months, Cohen's *d* (95% C.I.)	Main group effect, F (df = 1)	Group × time interaction, F (df = 2)	Effect size for group × time interaction, partial η^2
Parent self report										
Psychopathic personality inventory (PPI)										
PPI total	116.55 (11.36)	116.95 (9.68)	113.16 (12.67)[a]	108.44 (11.60)[a]	117.07 (12.14)[b]	108.11 (12.81)	−.72 (−1.00, −.43)	11.38**	13.97**	.07
PPI social potency	19.32 (3.79)	19.42 (3.77)	17.13 (4.29)[a]	17.67 (4.85)[a]	18.31 (4.70)[b]	17.08 (4.43)	−.27 (−.55, .01)	.14	5.98**	.03
PPI cold-heartedness	15.04 (3.84)	15.66 (3.08)	13.76 (3.76)[a]	14.27 (4.02)[a]	15.52 (4.28)[b]	15.39 (4.23)[b]	−.03 (−.31, .25)	.51	1.32	.01
PPI carefree nonplanfulness	11.30 (3.33)	12.93 (3.17)	10.16 (3.12)[a]	10.22 (2.89)[a]	11.57 (4.03)[b]	10.46 (3.18)	−.31 (−.58, −.03)	.30	13.29**	.06
PPI fearlessness	12.17 (3.94)	12.07 (3.12)	12.54 (5.32)	9.90 (3.33)[a]	12.95 (3.38)	11.07 (3.14)[b]	−.58 (−.86, −.29)	11.40**	14.43**	.07
PPI blame externalization	16.15 (6.70)	15.78 (6.07)	15.67 (7.25)	16.21 (6.70)	15.69 (6.73)	14.03 (6.82)[b]	−.25 (−.52, .03)	.32	7.21**	.04
PPI stress immunity	18.30 (3.37)	17.72 (2.67)	19.57 (3.89)[a]	17.60 (3.61)[a]	19.06 (3.46)	18.58 (3.26)[b]	−.14 (−.42, .13)	6.57*	6.13**	.03
PPI impulsive nonconformity	11.92 (3.17)	11.51 (2.84)	11.26 (3.42)[a]	10.14 (3.07)[a]	11.84 (3.28)	10.07 (3.09)	−.56 (−.84, −.27)	9.39**	4.41*	.02
PPI machiavellian egocentricity	12.35 (3.80)	11.89 (3.30)	13.07 (4.28)	12.43 (3.93)	12.12 (3.97)[b]	11.43 (3.40)[b]	−.19 (−.46, .09)	1.70	.12	.00
Reactive proactive aggression questionnaire										
RPQ proactive	.68 (1.41)	.54 (1.03)	.66 (1.26)	.39 (1.13)	.54 (2.08)	.37 (.65)	−.11 (−.39, .17)	1.52	.28	.00
RPQ reactive	4.45 (3.62)	5.25 (3.60)	4.17 (3.22)	4.84 (3.21)	3.82 (3.55)	3.72 (2.73)[b]	−.03 (−.31, .25)	1.21	3.15*	.02
RPQ total	5.13 (4.48)	5.79 (4.18)	4.83 (4.13)	5.23 (3.81)[a]	4.36 (5.11)	4.09 (3.09)[b]	−.06 (−.03, .21)	.25	2.21	.01

[a]Indicates within group behavior change from 0 to 6 months was statistically significant ($p < .05$).
[b]Indicates within group behavior change from 6 to 12 months was statistically significant ($p < .05$).

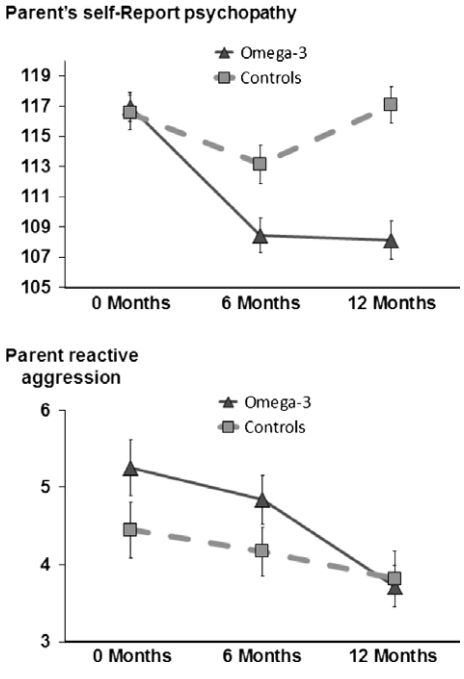

Figure 2 Significant group × time interactions (with standard error bars) for parents' self reports of their own psychopathy and reactive aggression

maker, 2006), overall the evidence from RCTs of omega-3 on depression is mixed (Giles, Mahoney, & Kanarek, 2013). Similar mixed conclusions have been drawn for omega-3 RCTs on ADHD, with some reviews suggesting small positive effects (Bloch & Qawasmi, 2011) while others suggest null results (Gillies, Sinn, Lad, Leach, & Ross, 2012). Clearly, the current findings on internalizing behavior must be treated with caution, while also suggesting that efficacy for internalizing behavior problems is worthy of further investigation.

Mechanisms of action

While the study cannot identify proximal neurobiological mechanisms whereby omega-3 results in long-term reductions in externalizing behavior problems, callous-unemotional traits, and reactive/proactive aggression, 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). In this context an RCT of omega-3 in children has been shown to enhance dorsolateral prefrontal functioning (McNamara & Carlson, 2006), a brain area found to be impaired in antisocial individuals (Fairchild et al., 2013; Seguin, Nagin, Assaad, & Tremblay, 2004; Yang & Raine, 2009). Future studies could therefore test the mediating hypothesis that omega-3 reduce antisocial behavior by enhancing prefrontal functioning.

Despite this study limitation, we were able to assess the mediating role of parental behavior on treatment efficacy. Giving children omega-3 resulted in improvements in their caregivers' antisocial behavior compared to controls. This parental improvement partly mediated improvements in child behavior produced by omega-3 supplementation. Specifically, reductions in parental psychopathy accounted for 60.9% of the improvement in child antisocial behavior. Because caregivers and their children have reciprocal effects on one another (Dodge & Pettit, 2003), it is not surprising to anticipate improvements in child behavior evoking improvement in parental behavior that further improves child behavior. Surprising however, no prior study of omega-3 on any child behavior has, to our knowledge, tested this reciprocity hypothesis. While initial, this finding highlights an intermediary parental behavioral mechanism for improved child behavior following omega-3 supplementation that requires further investigation.

Placebo effects

Improvements in child behavior were not explained by parent's belief in treatment allocation, with the group × time interaction effects remaining significant after controlling for this belief. On the contrary, effects for the narcissism component of the child psychopathy measure became significant after controlling for this confound. These findings dictate against a placebo effect as an explanation for the sustained improvement in child behavior over time.

Nevertheless, the placebo group did show improvements during the initial test period up to 6 months on several outcomes. While expectation of improvement with treatment enrollment likely contributed to this effect, it is also conceivable that the antioxidants and vitamin D contained in the placebo drink may have contributed to this transient change given some evidence suggesting potential efficacy of micronutrient supplementation for antisocial behavior (Benton, 2007).

Reporter effects

Improvement in child behavior following omega-3 consumption was observed for parent reports, but with the exception of proactive and reactive aggression, no effects were observed with child self reports. Similar results have been observed in other studies. The only two RCTs of omega-3 conducted in prison which documented behavioral improvement as monitored by others either failed to observe effects for self reports (Zaalberg et al., 2010) or did not report findings beyond baseline data (Gesch et al., 2002). Similarly Long and Benton (2013) found no effect of omega-3 on self-report aggression, but did find reduced aggression on a laboratory behavioral measure of aggression.

The fact that effects were nevertheless obtained for child self-reported proactive and reactive aggression

may be due to the fact that in the construction of this self-report measure, it was argued that children know better than their parents the underlying motive for aggressive behavior, a factor critical for distinguishing goal-oriented proactive aggression from aggression in reaction to a provocation (Raine et al., 2006). While the null results for other self report should be viewed as a limitation, from a clinical perspective the very large majority of clinic referrals for behavioral problems are from parents, not children. Consequently, the current findings for parental reports may have clinical relevance.

Study limitations and generalizability

Regarding limitations, the ITT approach which analyzed all participants irrespective of treatment completion is viewed as an important defense against selection bias (White et al., 2011) and is viewed as the primary approach to data analysis in RCTs (Hernan & Hernandez-Diaz, 2012). It is nevertheless believed to underestimate treatment effects in placebo-controlled RCTs (Hernan & Hernandez-Diaz, 2012). The sample size of 200 is not large, although given that more than 50% of all registered RCTs have fewer than 70 participants by design (Califf et al., 2012), the completed sample and associated statistical power compares favorably to other trials. While long-term posttreatment improvement was observed, we caution that this time period is 6 months and findings may or may not extend for longer. Furthermore, long-term effects were not observed for proactive and reactive aggression.

Caveats are also needed on generalizability of findings. While Mauritius is a developed country, future generalization to other countries and other ethnic groups is required. Furthermore, the research staff reported unusually strong enthusiasm to participate in this treatment study compared to the risk research normally conducted at the Joint Child Health Project. This again cautions against generalization of findings from this RCT to other international settings.

Conclusions

In conclusion, this RCT shows that 6 months of omega-3 supplementation in fruit juice drink form results in a 42–68% reduction in parent-reported externalizing and internalizing behavior problems in community-residing children and adolescents, with improvement continuing 6 months after treatment cessation. While replication and generalization to other countries is critical, the potential clinical promise is that these nutrients can shift the distribution of behavior problems to a lower level in the general population and that more severe behavioral problems that are significant risk factors for serious adult violence and psychopathology may be ameliorated.

Supporting information

Additional Supporting Information may be found in the online version of this article:

Table S1. CONSORT flow diagram.
Table S2. Minor adverse events.
Figure S1. Child proactive and reactive aggression.

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Key points

- It is unclear whether omega-3 supplementation can reduced externalizing and internalizing behavior problems in child and adolescent populations.
- This RCT showed that 6 months of omega-3 supplementation in fruit juice form produced long-term posttreatment reductions in parent-reported externalizing behavior problems (41.6%) and internalizing behavior problems (68.4%).
- Caregivers of children receiving omega-3 also showed significant reductions in their own antisocial behavior.
- Improvements in parental behavior accounted for 60.9% of the improvement in child behavior.
- This is the first study to report not just posttreatment reductions in child antisocial behavior, but also to document improvements in parental behavior that in part explain treatment efficacy.

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