Marine Omega-3 Fatty Acid Supplementation for Borderline Personality Disorder:
A Meta-Analysis

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ABSTRACT

Objective: Several promising studies investigated marine omega-3 fatty acids (ie, fish oil) in borderline personality disorder (BPD), but overall effects remain unclear. The aim of this study was to obtain estimates of effectiveness of omega-3 fatty acids in BPD using meta-analysis, with a priori differentiation of affective, impulsive, and cognitive-perceptual symptom domains.

Data Sources: We performed a literature search in PubMed, EMBASE, PsycINFO, and MEDLINE, using terms related to BPD and omega-3 fatty acids. Publication date was not a restriction.

Study Selection: We included randomized controlled trials (RCTs) that compared omega-3 fatty acids to placebo or any active comparator and pooled data using meta-analysis. Five studies were included in the meta-analysis, describing 4 RCTs testing effects of omega-3 fatty acids in 137 patients with BPD or BPD-related behavior.

Data Extraction: Using a pre-piloted data extraction form, we obtained data including intervention dose, duration, and BPD symptom scale scores, differentiating affective, impulsive, and cognitive-perceptual symptom domains.

Results: Random effects meta-analysis showed an overall significant decreasing effect of omega-3 fatty acids on overall BPD symptom severity (0.54 standardized difference in means [SDM]; 95% CI = 0.91 to 0.17; $Z = 2.87$; $P = .0041$), without heterogeneity ($I^2 = 0.00$; $Q = 2.63$; $P = .45$). A priori differentiation of relevant symptom domains showed significant effects on affect dysregulation (0.74 SDM; 95% CI = 1.21 to 0.27; $Z = 3.11$; $P = .002$) and impulsive behavior (0.45 SDM; 95% CI = 0.84 to 0.059; $Z = 2.26$; $P = .024$). However, effects on cognitive-perceptual symptoms did not reach the significance threshold.

Conclusions: Available data indicate that marine omega-3 fatty acids improve symptoms of BPD, particularly impulsive behavioral dyscontrol and affective dysregulation. Marine omega-3 fatty acids could be considered as add-on therapy.

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Borderline personality disorder (BPD) is characterized by impairments in self and interpersonal functioning, as presented by several symptom domains such as affective dysregulation, impulsive behavioral dyscontrol, and cognitive-perceptual symptoms.[1] With a ~1%–2% prevalence, BPD causes worldwide personal and societal suffering. Suicide rates in BPD are estimated to be up to 10%, accounting for 9%–33% of all suicides.[2] In addition, annual health care costs and productivity loss are comparable to those of schizophrenia (~€40.000 per patient).[3]

BPD guidelines prescribe several psycho- and pharmacotherapeutic treatments.[4] Effect sizes and levels of evidence of available psychotherapy studies vary and generally leave room for improvement. Pharmacotherapy is considered adjuvant, and there are no drugs approved for BPD, yet off-label polypharmacy is quite common. Differentiation according to cognitive-perceptual, affective, and impulsivity symptom domains showed differential effects of various drugs, as previously described in this journal.[5–7] Nevertheless, recent guidelines conclude that the evidence for efficacy of drugs in BPD is still very weak, and concerns are expressed for adverse effects, leading to the advice that pharmacologic treatment should be limited for BPD or not be used at all.[4] Altogether, there is an urgent need for improved BPD treatment with limited side effects.

Where traditional psychopharmacology mainly targets neurotransmitter systems, recent research suggests broader neurometabolic disturbances in psychiatric disorders, including in BPD. Neurometabolic network alterations in BPD have been shown in the hypothalamic-pituitary-adrenal (HPA) axis,[8,9] endocannabinoid system,[10] inflammatory[11] and antioxidant pathways,[12–14] brain-derived neurotrophic factor (BDNF), and brain structure and functional activity,[15] next to neurotransmitter dysfunction. These alterations seem partly mutually related and seem to reflect transdiagnostic symptom domains that can also explain the frequent comorbidity of mental disorders with BPD. Targeting these broader neurometabolic alterations may improve treatment of BPD.

An increasing amount of evidence suggests that these transdiagnostic alterations in neurometabolic networks can be effectively targeted using marine omega-3 polyunsaturated fatty acids (PUFAs), also known as fish oil.[16] Omega-3 PUFAs, including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), play a central neurometabolic role. They form essential components of (neuronal) membranes,[16] influencing brain structure and activity. In addition, they modulate membrane

Clinical Points

- Several promising studies investigated marine omega-3 fatty acids (ie, fish oil) in borderline personality disorder (BPD), but overall effects remain unclear. A meta-analysis was performed to inform clinicians and patients whether omega-3 polyunsaturated fatty acids may be a potential treatment option in BPD.
- Results from this meta-analysis indicate a beneficial effect of marine omega-3 fatty acid supplementation in BPD. Effects were particularly seen on affective dysregulation and impulsive behavior. Marine omega-3 fatty acids supplementation appears to be a potentially promising (add-on) intervention in the treatment of patients with BPD.

neurotransmitter receptors and release.[17] Moreover, PUFAs are involved in BDNF and endocannabinoid signaling and HPA axis regulation.[18] Finally, omega-3 PUFAs form precursors of anti-inflammatory eicosanoids.[19]

Importantly, human beings depend on dietary intake of omega-3 PUFAs, because we lack synthesizing capacity.[20] Our main dietary source of EPA and DHA is fatty fish. Fatty fish in turn obtain EPA and DHA from marine algae, which is why EPA and DHA can be called marine omega-3 PUFAs. There are other omega-3 PUFAs, but they have gained less scientific attention in psychiatry. The biological precursor of EPA and DHA, the omega-3 PUFA α linolenic acid (ALA), can be derived from plant seeds and nuts, but we have only limited capability to convert ALA into EPA and DHA, which seem to have more important biological effects in the neurometabolic pathophysiology of psychiatric disorders. Importantly, dietary omega-3 PUFA content has decreased substantially since the industrial revolution, therefore increasing the risk of deficiency. This is corroborated by associations of psychiatric disorders with decreased omega-3 PUFAs in diet and in blood samples.[16,21]

Several randomized controlled trials (RCTs) have investigated the effect of marine omega-3 PUFA supplementation in the treatment of various psychiatric disorders. Effects seem largest in major depressive disorder (MDD), in attention-deficit/hyperactivity disorder, and on aggressive behaviors.[22] Meta-analyses of RCTs in MDD suggest a clinically relevant effect, which led to the inclusion of marine omega-3 PUFAs (particularly EPA) in MDD treatment guidelines.[23] Effects seem largest in patients with increased inflammation markers receiving EPA, with a recommended dosage of 2,200 mg/d.[24]

In line with this growing evidence, several RCTs investigated marine omega-3 PUFAs in BPD. However, to the best of our knowledge, no meta-analysis of these studies has been performed yet. In the present study, we performed such a systematic review and meta-analysis to inform clinicians and patients whether omega-3 PUFAs may be a potential treatment option in BPD. We performed a priori specificity and sensitivity analyses, differentiating effects according to BPD relevant symptom domains and correcting for possible publication bias.

METHODS

Study Design

Following PRISMA guidelines,[25] prior to the beginning of the study the systematic review protocol was registered in PROSPERO.

Search Strategies

We performed a literature search in PubMed, Embase, PsycINFO, and MEDLINE, in line with earlier systematic reviews[26,27] (Supplementary Appendix 1). References of eligible studies were assessed for additional relevant studies. Publication date was not a restriction.

Study Selection

Two independent reviewers screened titles and abstracts of the found studies. Inconsistencies were solved by means of discussion, with a third reviewer whenever necessary. Studies were included if they were a randomized controlled trial investigating omega-3 fatty acids in participants diagnosed with borderline personality disorder. In order to include all potentially relevant evidence, we also included studies in which 70% of the participants fulfilled the diagnostic criteria for BPD according to the *Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV* or *-5* and randomized studies with an active control arm that lacked placebo control.

Critical Appraisal and Quality Assessment

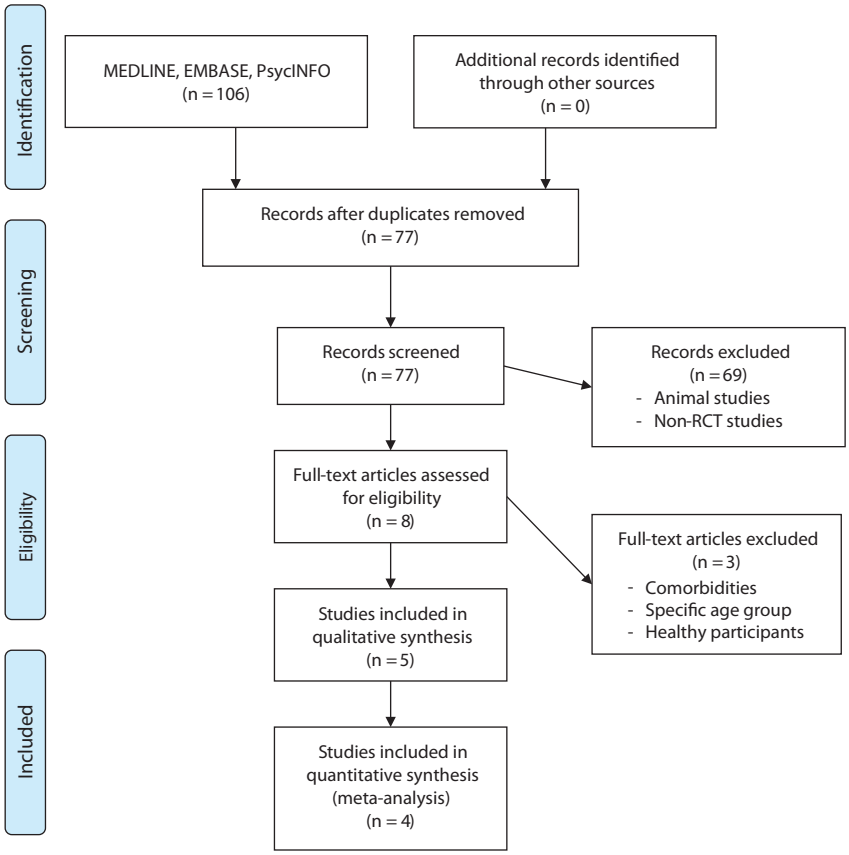
All included studies were critically appraised by means of the revised version of the Cochrane risk of bias tool.[28] In addition to the critical appraisal, the Grading of Recommendations Assessment Development and Evaluation (GRADE) methodology framework was used to systematically assess the quality of evidence.[29] The assessment of quality was rated by downgrading evidence by 1 level for serious concerns about study design, risk of bias, inconsistency, indirectness, imprecision, or publication bias. Inconsistencies between the two raters were solved by means of discussion.

Data Extraction and Outcome Data

Data were extracted using a standardized pre-piloted data extraction form. Only studies that reported their results in such a way that they could be included in the meta-analysis, or for which the researchers could provide these outcomes in response to our requests, were included.

The extracted data consisted of the following study characteristics: number of participants, number of time points, participants' characteristics (borderline personality disorder diagnosis at baseline), study duration, concomitant treatment, the intervention's components and dosages, and study outcome data. The outcome data were represented using several scales used by the studies to assess severity

Figure 1. PRISMA Flow Diagram for Included Studies



Abbreviation: RCT = randomized controlled trial.

of BPD symptoms and behavior before and/or after the interventions, including the Beck Depression Inventory,[30] Hamilton Depression Rating Scale,[31] Overt Aggression Scale (OAS),[32] Immediate and Delayed Memory Task,[33] Global Assessment of Functioning,[34] Positive and Negative Syndrome Scale (PANSS),[35] Montgomery-Asberg Depression Rating Scale (MADRS),[36] Borderline Personality Disorder Severity Index (BPDSI),[37] Hamilton Anxiety Rating Scale,[38] Barratt Impulsiveness Scale-11 (BIS-11),[39] Self-Harm Inventory,[40] Social and Occupational Functioning Assessment Scale (SOFAS),[41] and Clinical Global Impression—Severity of Illness scale (CGI-S).[42] For our main analyses, we used all relevant available BPD symptom severity outcome measures. In line with previous meta-analyses, we additionally determined differential effects on symptom domains, dividing borderline personality disorder symptoms into the following 3 domains: cognitive-perceptual symptoms, impulsive behavioral dyscontrol, and affective dysregulation, as well as global functioning.[43]

Outcome measures of the included studies were assigned to one of these domains as applicable. PANSS Positive and BPDSI Dissociation/Paranoid Ideation subscales were assigned to the cognitive-perceptual symptoms domain. BPDSI Parasuicidal Behaviors subscale, BIS-11, BPDSI Impulsivity subscale, OAS-Total, OAS-Aggression, OAS-Suicidality, and Self-Harm Inventory were assigned to the impulsive behavioral dyscontrol domain. Hamilton Anxiety Rating Scale, BPDSI Affective Instability, BPDSI-Anger, Beck Depression Inventory, Hamilton Depression Rating Scale, MADRS, and OAS-Irritability were assigned to the affective dysregulation domain. Moreover, CGI-S, Global Assessment of Functioning, and SOFAS were assigned to the global functioning domain, ie, well-being.

Statistical Analyses

Main analyses. Comprehensive Meta-Analysis V3 was used to perform a quantitative data synthesis using random effects models. Two-tailed *P* values and 95% confidence intervals were used. For continuous results, standardized mean difference (SMD) was used. To estimate the heterogeneity between included studies, I^2 statistics were calculated. I^2 values greater than 50% implied substantial heterogeneity. Sensitivity analyses were performed using post intervention data only.

Publication bias. Publication bias was assessed by plotting a funnel plot. The classic and Orwin fail-safe N, Begg and Mazumdar rank correlation, and Egger regression intercept are reported. The Duval and Tweedie trim-and-fill method was used to report adjusted values, if necessary.[27]

Meta-regression. We intended to perform meta-regression for effects of EPA and DHA dose and study

Table 1. Study Characteristics of Included Studies

First author	Year	Population	N	Omega-3 intervention	Control	Supplementation length	Outcome	Analyses	Other
Hallahan[47]	2007	Patients with recurrent self-harm	Total: 49 EPA + DHA: 22 C: 27	1,220 mg EPA and 908 mg DHA	Placebo: 99% corn oil and 1% EPA/DHA mixture	12 wk	BDI, HDRS, OAS, 12 wk	ITT	
Zanarini[44]	2003	Women with BPD	Total: 30 E-EPA: 20 C: 10	1,000 mg of 97% E-EPA	Placebo: mineral oil	8 wk	MOAS, MADRS, 8 wk	mITT, LOCF	Subjects were excluded if they were taking psychotropic medication
Amminger[48]	2013	Adolescents with BPD	Total: 15 EPA + DHA: 8 C: 7	700 mg EPA, 480 mg DHA, 7.6 mg vitamin E	Placebo: coconut oil, 7.6 mg vitamin E, 1% fish oil	12 wk	PANSS, MADRS, GAF, 12 wk	ITT	Subjects were excluded if they had a history of a treatment with antipsychotics or mood stabilizers
Bellino[45]	2014	Consecutive outpatients with a diagnosis of BPD	Total: 34 EPA + DHA: 18 C: 16	1,200 mg EPA, 800 mg DHA, 50–100 µg/mL valproic acid	Valproic acid 50–100 µg/mL	12 wk	HDRS, HARS, BPDSI, BIS-11, MOAS, SHI, SOFAS, CGI-S, 12 wk	PP	Subjects were excluded if they were taking psychotropic medications in 2 months preceding the beginning of study. Follow-up in Bozzatello et al 2018[46]

Abbreviations: BDI = Beck Depression Inventory, BIS-11 = Barratt Impulsiveness Scale, BPDSI = Borderline Personality Disorder Severity Index, C = control subjects, CGI-S = Clinical Global Impression—Severity of Illness scale, DHA = docosahexaenoic acid, EPA = eicosapentaenoic acid, GAF = Global Assessment of Functioning, HARS = Hamilton Anxiety Rating Scale, HDRS = Hamilton Rating Depression Scale, ITT = intention to treat, LOCF = last observation carried forward, MADRS = Montgomery-Asberg Depression Rating Scale, mITT = modified intention to treat, MOAS = Modified Overt Aggression Scale, OAS = Overt Aggression Scale, N = number of subjects, PANSS = Positive and Negative Syndrome Scale, PP = per protocol, SHI = Self-Harm Inventory, SOFAS = Social and Occupational Functioning Assessment Scale.

duration, but too little heterogeneity existed between studies, resulting in inadequate power for meta-regression.

RESULTS

Study Selection

The literature search provided a set of 77 unique articles. After screening titles and abstracts, 69 articles were excluded. After full texts of the remaining 8 articles were assessed, 5 studies were included for the quantitative analysis. Since 2 studies report on the same RCT, 4 unique RCTs were included for the meta-analysis. Figure 1 shows details of the study selection process.

Study Characteristics

The 4 RCTs included 137 participants. Three RCTs included patients with BPD, and 1 RCT included subjects with recurrent self-harm, of which 71% were diagnosed with BPD. Overall, 89.8% (123/137) of the participants were diagnosed with BPD; the remaining 10.2% (14/137) were diagnosed with paranoid personality disorder. 79.7% (102/128) of the participants were female. One study[44] used omega-3 fatty acids as monotherapy. The other studies used omega-3 fatty acids as add-on therapy to antidepressants, benzodiazepines, and/or valproic acid. There were no studies that included patients using antipsychotics.

All RCTs studied marine omega-3 PUFAs EPA and/or DHA, and there were no studies on plant-derived omega-3 interventions such as ALA. The EPA doses varied between 700–1,200 mg/d, DHA between 0–908 mg/d. Most studies used scales to determine depression, impulsivity, and/or aggression. Three studies compared omega-3 fatty acids to placebo; however, 1 RCT[45,46] compared the combination of marine omega-3 fatty acids and valproic acid to valproic acid monotherapy, lacking a placebo control. Table 1 shows characteristics of all included studies.

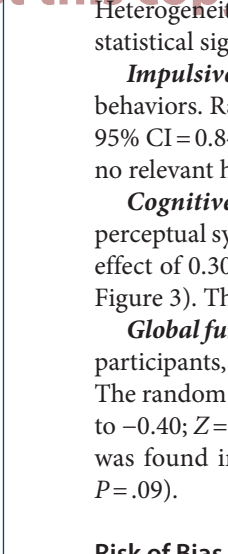
Main Analyses

Random effects meta-analysis of all 4 RCTs, provided a significant main effect of 0.54 (standardized difference in means [SDM]; 95% CI = 0.91 to 0.17; $Z = 2.87$; $P = .0041$; Figure 2). This shows that the overall decreasing effect of omega-3 fatty acids on symptom severity related to BPD is significantly larger than in the control group, with a medium effect size. There was no relevant heterogeneity ($I^2 = 0.00$; $Q = 2.63$; $P = .45$).

Effects on Symptom Domains

Affective dysregulation. Four RCTs[44–48] assessed symptoms related to affective dysregulation. Random effects analyses showed a main effect of 0.74 (SDM; 95% CI = 1.21 to 0.27; $Z = 3.11$; $P = .002$; Supplementary Figure 1).

Figure 2. Forest Plot Showing the Meta-Analysis of the Included Randomized Controlled Trials Showing the Effect of Omega-3 Fatty Acid Supplementation vs Control on Overall Borderline Personality Disorder Symptom Severity (N = 137)[44–48]



Model	Study name	Outcome	Comparison	Time point (wk)	Std diff in means	Standard error	Statistics for each study: Variance	Lower limit	Upper limit	Z value	P value
	Hallahan 2007[47]	Combined	EPA+DHA vs placebo	Combined	0.3979	0.2914	0.0849	−0.1732	0.9690	1.3655	.1721
	Zanarini 2003[44]	Combined	EPA+DHA vs placebo	8	0.1811	0.4093	0.1675	−0.6211	0.9833	0.4425	.6581
	Amminger 2013[48]	Combined	EPA+DHA vs placebo	12	1.1069	0.5569	0.3101	0.0155	2.1984	1.9878	.0468
	Bellino 2014[45]	Combined	Combined	Combined	0.8264	0.3748	0.1405	0.0918	1.5610	2.2048	.0275
Fixed					0.5418	0.1887	0.0356	0.1720	0.9116	2.8715	.0041
Random					0.5418	0.1887	0.0356	0.1720	0.9116	2.8715	.0041

Abbreviations: DHA = docosahexaenoic acid, EPA = eicosapentaenoic acid, std diff = standard difference.

Heterogeneity was more pronounced in this symptom group but did not reach statistical significance ($I^2 = 31.24$; $Q = 4.36$; $P = .23$).

Impulsive behavioral dyscontrol. Three RCTs[44–47] assessed impulsive behaviors. Random effects meta-analysis showed a main effect of 0.45 (SDM; 95% CI = 0.84 to 0.059; $Z = 2.26$; $P = .024$; Supplementary Figure 2). There was no relevant heterogeneity ($I^2 = 0.00$; $Q = 1.64$; $P = .44$).

Cognitive-perceptual symptoms. Two RCTs[45,46,48] assessed cognitive-perceptual symptoms. Random effects analyses showed a main nonsignificant effect of 0.30 (SDM; 95% CI = 0.96 to −0.36; $Z = 0.88$; $P = .38$; Supplementary Figure 3). There was no relevant heterogeneity ($I^2 = 20.47$; $Q = 1.26$; $P = .26$).

Global functioning. Two RCTs[45,46,48] assessed the global functioning of the participants, including CGI-S, Global Assessment of Functioning, and SOFAS. The random effects analyses showed a main effect of 0.70 (SDM; 95% CI; 1.80 to −0.40; $Z = 1.25$; $P = .21$; Supplementary Figure 4). Substantial heterogeneity was found in the global functioning symptom group ($I^2 = 65.17$; $Q = 2.87$; $P = .09$).

Risk of Bias and Quality of Evidence

The risk of bias summary is shown in Supplementary Figure 5. Some biases remained unclear because of the absence of pre-published trial protocols. As noted above, 1 RCT[45,46] had no placebo control, potentially leading to biases. Another RCT[48] showed evidence for selective reporting, in that subjects who had experienced a psychotic decompensation were excluded from follow-up. No other clear evidence for biases was found.

Table 2 shows details of the quality assessment. Overall, there is moderate quality evidence that omega-3 fatty acids supplementation is effective in patients suffering from borderline personality disorder, particularly symptoms related to impulsive behaviors and affective dysregulation. For cognitive-perceptual symptoms and global functioning, the quality of evidence is still low and very low, respectively.

Sensitivity Analyses

Post-intervention data. The random effects sensitivity analyses using post-intervention data showed a main effect of 0.46 (SDM; 95% CI = 0.83 to 0.097; $Z = 2.48$; $P = .013$).

Participants with borderline personality disorder vs non-diagnosed participants. Random effects sensitivity analysis excluding the one study in which not all subjects were diagnosed with BPD[47] reported a main effect of 0.65 (SDM; 95% CI = 1.16 to 0.14; $Z = 2.48$; $P = .013$).

Placebo vs valproic acid. The random effects sensitivity analysis including only studies comparing omega-3 fatty acids to placebo (excluding the RCT comparing to valproic acid monotherapy[45,46]) reported a main effect of 0.45 (SDM; 95% CI = 0.87 to 0.017; $Z = 2.04$; $P = .041$).

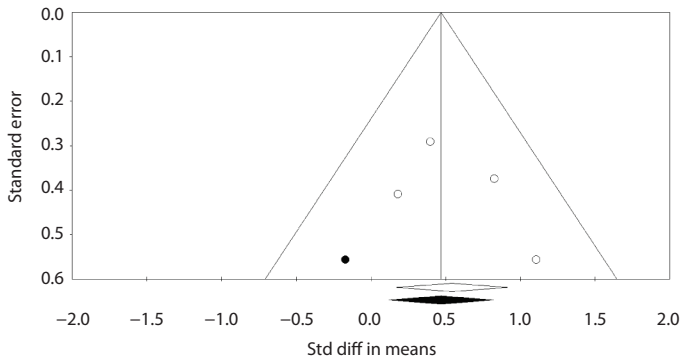
Publication bias. The classic fail-safe N was 6, and the Orwin fail-safe N was 11 with criterion for a "trivial" standardized difference in means as 0.15 and mean standardized difference in means in missing studies as 0. This suggested that at least 11 studies without any effect must have been reported to decrease the overall effect to a trivial effect. Concerning the Begg and Mazumdar rank-correlation test, Kendall tau with continuity correction was 0.17 ($P_{2\text{-sided}} = .73$) and without continuity correction was 0.33 ($P_{2\text{-sided}} = .50$), suggesting no publication bias. Egger regression intercept was 2.05 (95% CI = −7.23 to 11.33; $P_{2\text{-sided}} = .44$), also indicating no publication bias. The Duval and Tweedie trim-and-fill method, which used the random-effects model looking for missing studies to the left of the mean, meaning a less favorable effect of omega-3 fatty acids supplementation, showed 1 study that needed to be trimmed. This, however, had only limited influence on the effect estimate, with a comparable effect size of 0.47 (SDM; 95% CI = 0.11 to 0.82). Figure 3 shows the values of

Table 2. Quality of the Evidence of Analyses on the Effect of PUFAs on Borderline Personality Disorder

Analysis	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Effect size	Final GRADE score
Overall	+4, RCTs	−1	0, no heterogeneity	0	0	0, undetected	0	⊕⊕⊕⊖ moderate
Cognitive-perceptual symptoms	+4, RCTs	−1	0, no heterogeneity	0	−1, imprecision	0, undetected	0	⊕⊕⊖⊖ low
Impulsive behavioral dyscontrol	+4, RCTs	−1	0, no heterogeneity	0	0	0, undetected	0	⊕⊕⊕⊖ moderate
Affective dysregulation	+4, RCTs	−1	0, no heterogeneity	0	0	0, undetected	0	⊕⊕⊕⊖ moderate
Global functioning	+4, RCTs	−1	−1, heterogeneity	0	−1, imprecision	0, undetected	0	⊕⊖⊖⊖ very low

Abbreviations: GRADE = Grading of Recommendations Assessment, Development, and Evaluation; PUFA = polyunsaturated fatty acid; RCT = randomized controlled trial.

Figure 3. Funnel Plot of Standard Error by Standardized Difference in Means Showing Values of the Duval and Tweedie Trim-And-Fill Method[a]



[a]Open circles are observed data points; closed circles are data points filled by the Duval and Tweedie trim-and-fill method. The open diamond indicates the standard difference in means (SDM) with 95% CI, and the filled diamond is the SDM and 95% CI after the trim-and-fill method.
Abbreviation: std diff = standard difference.

the Duval and Tweedie trim-and-fill method. Using a fixed effect model that is more sensitive for publication bias, the resulting point estimate did not change.

DISCUSSION

This meta-analysis pooled all available evidence on efficacy of omega-3 fatty acids for borderline personality disorder. By combining results of 5 papers reporting on 4 RCTs with a total number of 137 patients, random effects meta-analysis showed an overall beneficial effect with a medium effect size of 0.54. A priori differentiation according to symptom domains showed that particularly impulsive behavioral dyscontrol and affective dysregulation improved with marine omega-3 fatty acid supplementation. There was limited evidence for publication bias, correction of which did not result in fundamental changes in effect estimates. The quality of the evidence was considered moderate, mostly due to lack of pre-published trial protocols. These findings suggest that marine omega-3 fatty acid supplementation could be a viable supplemental treatment option for BPD patients.

Effects of marine omega-3 fatty acids in this meta-analysis were particularly seen on impulsive and affective symptoms, in line with effectiveness in other mental disorders. For instance, omega-3 fatty acids decreased feelings of anger in substance abusers,[49] and decreased aggression was found after PUFAs supplementation in healthy participants.[50] In the same study, omega-3 fatty acids supplementation attenuated impulsivity especially in the initially more impulsive subjects.[50] Meta-analyses also showed effectiveness of omega-3 fatty acids in affective disorders including MDD and peripartum depression.[27,51]

These effects of omega-3 fatty acids on impulsivity and affective dysregulation may be explained through the anti-inflammatory actions of their metabolites. Both impulsivity and affective disorders have been linked to increased inflammation,[52–54] which has also been shown in BPD patients.[13] Omega-3 fatty acids, particularly EPA, have been shown to decrease inflammatory activity,[19] potentially ameliorating inflammation-mediated increases in impulsiveness and affective dysregulation.

On the other hand, our meta-analysis showed no clear effect of marine omega-3 PUFAs on cognitive-perceptual symptoms and global functioning. While the literature overall shows less evidence for an effect of PUFAs on cognitive-perceptual symptoms, some studies do provide evidence for a beneficial effect of omega-3 fatty acids on perceptual symptoms in schizophrenia, but only as add-on therapy.[55,56] One explanation for differences in effects on affective/impulsive vs cognitive-perceptual symptoms may be an interaction with concomitant psychopharmacologic treatment. P-glycoprotein is an efflux transporter that removes drugs over the blood-brain barrier and that seems to be activated by inflammation.[57] Lowering inflammation by omega-3 fatty acid supplementation could therefore result in decreased P-glycoprotein activity and thereby higher drug concentrations in the brain.[58,59] Although both antidepressant and antipsychotic action could benefit from this effect,[60,61] the studies included in our meta-analysis did not include patients that used antipsychotics. This may suggest that omega-3 supplementation enhanced the effects

of antidepressants on impulsivity and affective dysregulation, but in our meta-analysis could not enhance effects of antipsychotics, which are commonly used in clinical practice for cognitive-perceptual symptoms in BPD.

Limitations and Strengths

Although there was only limited evidence for important study bias or publication bias, some biases could not be assessed and remained unclear, eg, because pre-published protocols were not available. In addition, although we included all available evidence, the overall N was still modest. Nevertheless, a low heterogeneity resulted in relatively precise effect estimates. However, the promising findings urge for larger studies, eg, to investigate factors that predict and mediate response. Furthermore, we included a study that used no placebo control (during treatment with valproic acid). This may have affected the overall effect size. Yet, it enabled us to include all available data. Moreover, sensitivity analyses including only comparisons to placebo resulted in a similar effect size. Finally, studies did not report blind guess rates, potentially inducing bias as with other studies in this field. However, studies tried to minimize the difference in taste between fish oil and placebo, by adding a small amount of fish oil to the placebo.

Major strengths of this study were that it is the first comprehensive systematic review and meta-analysis on omega-3 fatty acids for BPD and that we included all available outcomes in our analyses, which facilitated a priori differentiation according to BPD relevant symptom domains.

Research Implications

Findings of this meta-analysis suggest that interventions such as marine omega-3 fatty acids, targeted at neurometabolic alterations, may be a viable supplemental or add-on treatment option in BPD. More insight in neurometabolic disturbances in BPD patients, eg, using lipidomics or metabolomics, may illuminate the specific pathways that should be targeted. Moreover, the relation between omega-3 fatty acids, inflammation, P-glycoprotein, and psychopharmacologic effects of antidepressants, mood stabilizers, or antipsychotics may deserve further attention. These factors could be assessed in future trials in order to better predict effects of interventions and/or enhance treatment effectiveness.

Clinical Implications

The present meta-analysis shows moderate quality evidence for a beneficial effect of marine omega-3 fatty acids on BDP, with a moderate effect size. With regard to clinical recommendations, it is important to note that the quality of evidence and effect sizes of other currently available treatment options in BPD are also still limited. Moreover, marine omega-3 fatty acids could be provided as add-on therapy with a relatively safe side effect profile. Side effects include gastrointestinal complaints that are mostly mild and an increased bleeding tendency that may necessitate dose adjustment of anticoagulant drugs. All in all, we suggest that marine omega-3 fatty acids could be presented as an (add-on) treatment option for BPD-patients in a shared decision-making context. As with all supplement interventions, it is important to stress that they do not form an alternative to a healthy diet and lifestyle, and they are not free from side effects, although side effects are generally considered manageable. Clinically relevant effects could be particularly expected on impulsivity and affective symptom domains.

CONCLUSION

Results from this meta-analysis indicate a beneficial effect of marine omega-3 fatty acid supplementation in borderline personality disorder. Effects were particularly seen on affective dysregulation and impulsive behavior. Quality of the evidence and the effect size were moderate. All in all, marine omega-3 fatty acids supplementation appears to be a potentially promising (add-on) intervention in the treatment of relevant symptom domains in patients with borderline personality disorder.

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Supplementary Material

Article Title: Marine Omega-3 Fatty Acid Supplementation for Borderline Personality Disorder: A Meta-Analysis

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List of Supplementary Material for the article

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2. Figure 2 — Forest Plot Showing Meta-Analysis Effects of Omega-3 Fatty Acid Supplementation on Impulsive Behavioral Dyscontrol Symptoms vs. Control for Borderline Personality Disorder (N=122)
3. Figure 3 — Forest Plot Showing Meta-Analysis Effects of Omega-3 Fatty Acid Supplementation on Cognitive-Perceptual Symptoms vs. Control for Borderline Personality Disorder (N=58)
4. Figure 4 — Forest Plot Showing Effects of Omega-3 Fatty Acid Supplementation on Global Functioning vs. Control for Borderline Personality Disorder (N=58)
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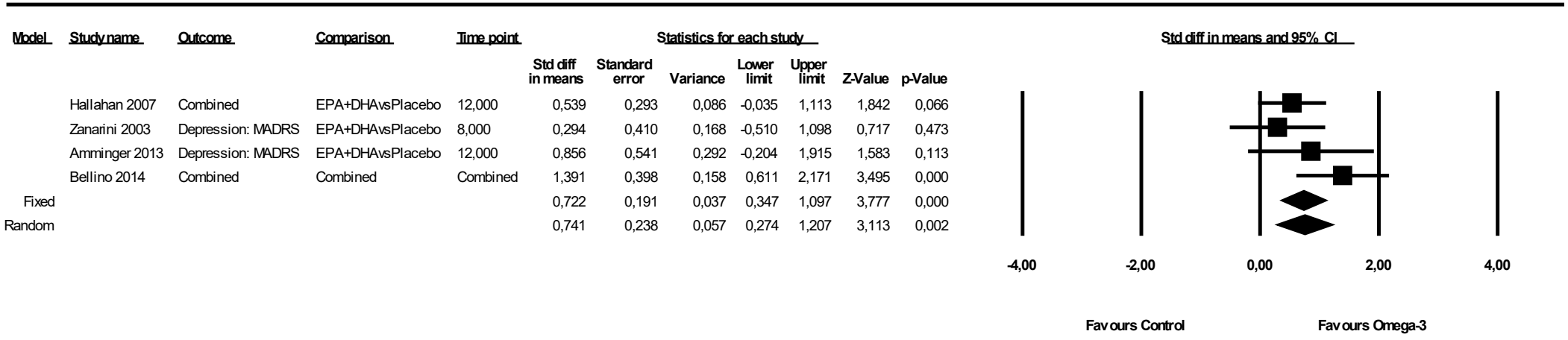
Supplementary Figure 1. Forest plot showing meta-analysis effects of omega-3 fatty acid supplementation on affective dysregulation symptoms[a] vs. control for borderline personality disorder (N=137)[44-48].

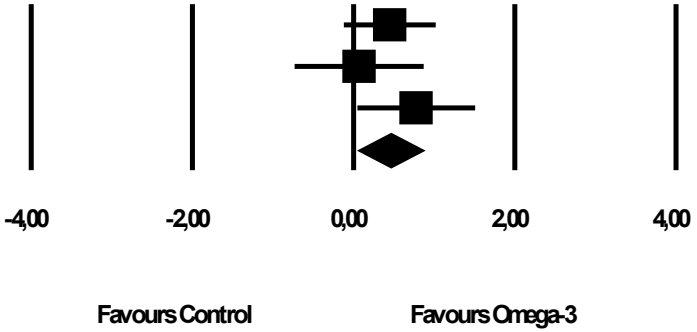


Model	Study name	Outcome	Comparison	Time point	Statistics for each study						
					Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
	Hallahan 2007	Combined	EPA+DHAvsPlacebo	12,000	0,539	0,293	0,086	-0,035	1,113	1,842	0,066
	Zanarini 2003	Depression: MADRS	EPA+DHAvsPlacebo	8,000	0,294	0,410	0,168	-0,510	1,098	0,717	0,473
	Amminger 2013	Depression: MADRS	EPA+DHAvsPlacebo	12,000	0,856	0,541	0,292	-0,204	1,915	1,583	0,113
	Bellino 2014	Combined	Combined	Combined	1,391	0,398	0,158	0,611	2,171	3,495	0,000
Fixed					0,722	0,191	0,037	0,347	1,097	3,777	0,000
Random					0,741	0,238	0,057	0,274	1,207	3,113	0,002

[a]Outcome measures of the included studies were assigned to one of these domains as applicable. Hamilton-anxiety, BPDSI Affective instability, BPDSI-Anger, Beck-Depression, Hamilton-Depression, MADRS and OAS-Irritability were assigned to affective dysregulation domain.

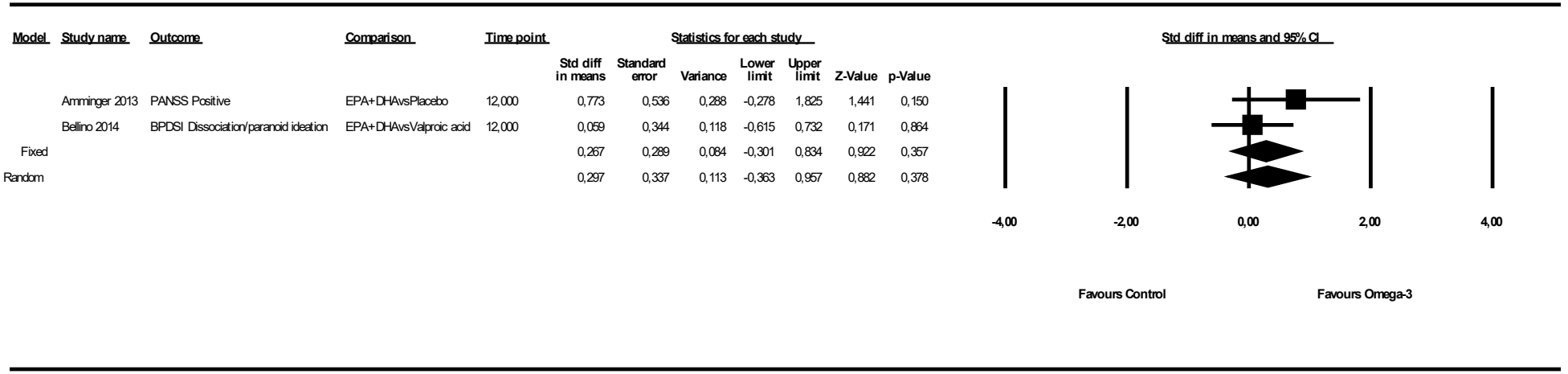
Supplementary Figure 2. Forest plot showing meta-analysis effects of omega-3 fatty acid supplementation on impulsive behavioral dyscontrol symptoms[a] vs. control for borderline personality disorder (N=122)[44-47].

Study name	Outcome	Comparison	Time point	Statistics for each study						
				Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Hallahan 2007	Combined	EPA+DHA vs Placebo	12,000	0,448	0,291	0,085	-0,123	1,018	1,538	0,124
Zanarini 2003	OAS	EPA+DHA vs Placebo	8,000	0,068	0,408	0,167	-0,732	0,868	0,167	0,868
Bellino 2014	Combined	Combined	Combined	0,777	0,373	0,139	0,046	1,508	2,082	0,037
				0,451	0,200	0,040	0,059	0,843	2,255	0,024



[a]Outcome measures of the included studies were assigned to one of these domains as applicable. BPDSI Parasuicidal behaviors subscale, BIS-11, BPDSI Impulsivity subscale, OAS-total, OAS-Aggression, OAS-Suicidality and Self-Harm Inventory were assigned to impulsive behavior domain.

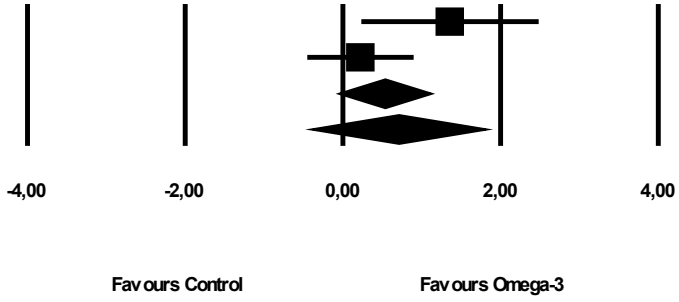
Supplementary Figure 3. Forest plot showing meta-analysis effects of omega-3 fatty acid supplementation on cognitive-perceptual symptoms[a] vs. control for borderline personality disorder (N=58)[45, 46, 48].



[a]Outcome measures of the included studies were assigned to one of these domains as applicable. PANSS Positive and BPDSI Dissociation/Paranoid ideation subscale were assigned to cognitive-perceptual symptoms domain.

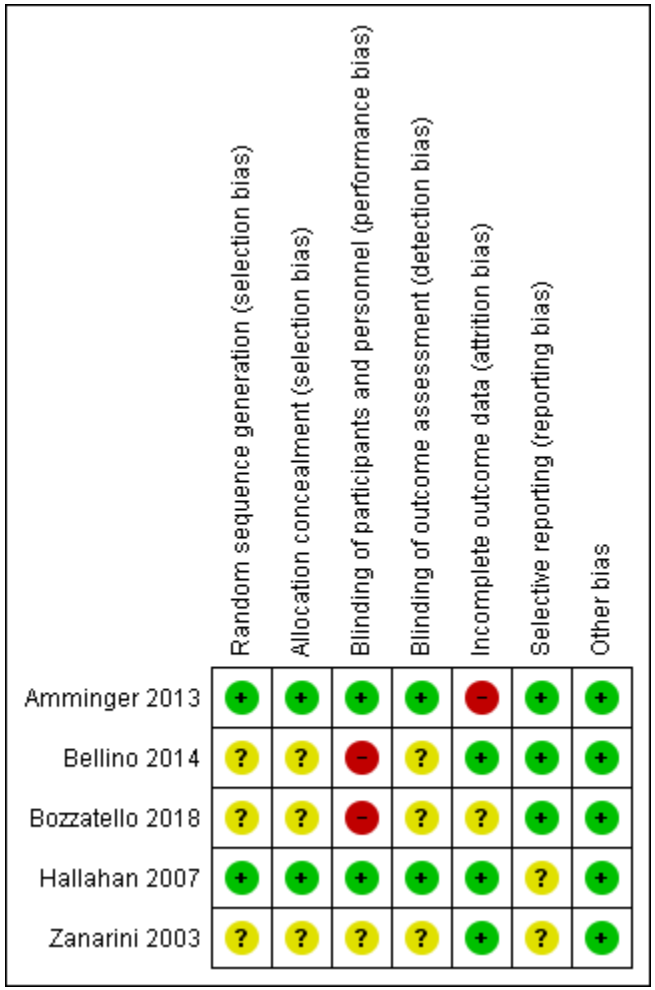
Supplementary Figure 4. Forest plot showing effects of omega-3 fatty acid supplementation on global functioning[a] vs. control for borderline personality disorder (N=58)[45, 46, 48].

Model	Study name	Outcome	Comparison	Time point	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
	Amminger 2013	GAF	EPA+DHAvsPlacebo	12,000	1,357	0,574	0,329	0,232	2,482	2,365	0,018
	Bellino 2014	Combined	EPA+DHAvsValproic acid	12,000	0,223	0,345	0,119	-0,453	0,898	0,646	0,518
Fixed					0,524	0,295	0,087	-0,056	1,103	1,772	0,076
Random					0,697	0,559	0,313	-0,399	1,794	1,246	0,213



[a]Outcome measures of the included studies were assigned to one of these domains as applicable. CGI-S, Global Assessment of Functioning and SOFAS were assigned to global functioning domain, i.e. well-being.

Supplementary Figure 5. Risk of bias summary of included studies



Appendix 1. Search (MEDLINE, Embase, PsycINFO)

1 Borderline Personality Disorder/

2 ((borderline or border-line) adj3 (state* or personalit*)).kf,tw.

3 ("Axis II" or "Cluster B" or flamboyant or "F60.3" or "F60.30" or "F60.31").kf,tw.

4 (idealization adj5 devaluation).kf,tw.

5 ((vulnerable or hyperbolic) adj3 temperament).kf,tw.

6 (((unstab* or instab* or poor or disturb* or fail* or weak or dysregulat*) adj3 (self* or impuls* or interperson* or identit* or relationship* or emotion* or affect*)) and (personality or character or PD)).kf,tw.

7 (impulsiv* adj5 (behavio?r or character or personalit*)).kf,tw.

8 (self adj3 (injur* or damag* or destruct* or harm* or hurt* or mutilat*)).kf,tw.

9 (suicidal adj3 behavio?r).kf,tw.

10 (feel* adj3 (empt* or bored*)).kf,tw.

11 (anger adj5 control*).kf,tw.

12 (risk-taking adj3 behavio?r).kf,tw.

13 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12

14 randomized controlled trial.pt.

15 controlled clinical trial.pt.

16 randomi#ed.ab.

17 placebo.ab.

18 randomly.ab.

19 trial.ab.

20 groups.ab.

21 drug therapy.fs.

22 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21

23 13 and 22

24 exp animals/

25 humans/

26 24 not 25

27 23 not 26

28 fish oils/

29 fatty acids, omega 3/ 30 omega-3.ab,tw.

31 polyunsaturated FA.ab,tw.

32 fish oil.tw,ab.

33 EPA.tw,ab.

34 DHA.tw,ab.

35 eicosapentaenoic acid.tw,ab.

36 docosahexaenoic acid.tw,ab.

37 alpha-linolenic acid.tw,ab.

38 cod liver oil.tw,ab.

39 n-3 fatty acids.tw,ab.

40 n3 polyunsaturated fatty acids.tw,ab.

41 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 42 27 and 41