REVIEW

Effects of Fish-Oil Consumption on Psychological Function Outcomes in Psychosis: A Systematic Review and Dose–Response Meta-Analysis of Randomized Controlled Trials

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ABSTRACT

Research on the effects of fish oil on clinical symptoms and psychosocial functioning in people with psychosis has been inconsistent. We conducted this systematic review and meta-analysis to summarize the available data on the effects of oral intake of fish oil on psychological functioning in patients with psychosis. Three online databases including PubMed, Scopus, and Web of Science were searched to identify relevant studies published by April 2021. The exposure was oral fish-oil supplementation. The Positive and Negative Syndrome Scale (PANSS), the Brief Psychiatric Rating Scale (BPRS), and the Global Assessment of Functioning (GAF) were our outcome measures. Seventeen randomized clinical trials involving 1390 patients were included. No change in PANSS was observed following oral fish-oil intake [weighted mean difference (WMD): −0.87; 95% CI: −16.99, 15.26; $P = 0.92$]. In a nonlinear dose–response analysis, a significant inverse association was observed between <10 wk of fish-oil supplementation and PANSS (WMD: −10; *P*-nonlinearity = 0.02). Although analysis of 4 studies showed a nonsignificant reduction in BPRS after fish-oil intake (WMD: −2.990; 95% CI: −6.42, 0.44; $P = 0.08$), a nonlinear dose–response analysis revealed significant inverse associations between dose (>2200 mg/d) and duration of fish-oil supplementation (<15 wk) with BPRS score (WMD: −8; *P*-nonlinearity = 0.04). Combined effect sizes from 6 randomized clinical trials showed significant increases in GAF after oral administration of fish oil (WMD: 6.66; 95% CI: 3.39, 9.93; $P < 0.001$). In conclusion, we did not find any significant changes in PANSS and BPRS scores following fish-oil supplementation. Nevertheless, oral fish-oil intake significantly contributed to improvement in GAF scores. This is the first meta-analysis to examine the effects of fish oil on the psychological functioning scores of PANSS, BPRS, and GAF simultaneously. *Adv Nutr* 2022;13:2149–2164.

Statement of Significance: Given ongoing progress in the treatment of psychotic disorders such as schizophrenia, this meta-analysis of randomized clinical trials, which suggests fish oil as a complementary agent to routine treatment, may be helpful to improve functioning in patients with psychosis.

Keywords: fish oil, psychosis, PANSS, BPRS, GAF

Introduction

Mental disorders are prevalent worldwide and have adverse effects on health, social, and economic conditions (1, 2). Globally, approximately 0.4% of the population suffers from psychosis (3). Furthermore, the prevalence of schizophrenia and related psychotic diseases in the United States is estimated to be between 0.25% and 0.64% (4–6). Psychosis can lead to mental conditions such as schizophrenia, bipolar disorder, and major depression (7).

The mechanism by which omega-3 fatty acids affect mental illness has not been conclusively determined. Possible mechanisms include their effects on inflammatory factors, brain-derived neurotrophic factor (BDNF), cardiovascular factors, cortisol (8, 9), and brain development as well as

prostaglandins and dopaminergic inhibition (10–12). EPA, with its antagonistic role in the production of prostaglandin E2, may improve motor function (13). DHA and EPA are essential for receptor binding, signal transduction, and neurotransmission as well as cognitive functions such as memory and learning (14–16). The ratio of ω-6 to ω-3 fatty acids in RBC membranes is also associated with symptoms of psychosis and depression (17). Long-chain ω-3 fatty acids improve performance and reduce psychological symptoms (18). Hence, studying the homeostasis of PUFAs is vital to identify nutritional strategies to alter the development and progression of schizophrenia.

The Positive and Negative Syndrome Scale (PANSS), known as the gold standard for the assessment of psychotic disorders, is a multidimensional scoring system of symptoms (including positive, negative, and general psychopathology scales), which is obtained through structured interviews with patients, health care providers, and family member reports (19, 20). The Brief Psychiatric Rating Scale (BPRS) is one of the first and most widely used tools for assessing the symptoms of psychosis and provides a rapid assessment of the presence and severity of symptoms (21). The 24-item BPRS score is based on a semi-structured interview that includes more detail about each symptom compared with earlier versions (22). The Global Assessment of Functioning (GAF) score, based on the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* (DSM-IV-TR), subjectively evaluates an individual's psychological, occupational, and social performance (23).

Findings regarding the effects of fish oil on psychological function in psychosis have been contradictory. Some studies have observed protective effects of fish oil on BPRS, PANSS, and GAF (17, 18, 24–27). However, other studies have not observed significant associations (28–34). Therefore, since no comprehensive systematic review and meta-analysis has been performed on psychological functioning outcomes among people with psychosis, we conducted the present meta-analysis to investigate and summarize the available data on the effects of fish oil on psychopathology and functioning in patients with psychosis.

Methods

Search strategy

This study was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and followed the Cochrane Handbook for Systematic Reviews of Interventions (35). We reviewed clinical trials on the effects of fish oil on functional factors in psychosis. To identify relevant studies, we searched 3 electronic databases including PubMed/Medline, Scopus, and Web of Science. The keywords used to search these databases were selected from the Medical Subject Headings (MeSH) database. We also used keywords from previous meta-analyses on psychosis. The search strategy for each database is presented separately in the **Supplemental Methods**. There were no restrictions on the time of article publication. All articles published by April 2021 were reviewed. We also had no restrictions on the language of publication. The reference lists of the included articles were also searched manually. Unpublished studies and gray literature, such as dissertations and conference papers and patents, were not included. In cases where there was no access to the full text of the articles or dissertations, we sought to access the full article and results via e-mail with the corresponding author.

Study selection and inclusion and exclusion criteria

Inclusion criteria.

All randomized clinical trials that examined the effect of oral fish oil on functional factors in patients with psychosis were included. We selected studies on patients with schizophrenia, schizoaffective disorder, and other diseases with symptoms of psychosis. Publications that reported the effect size as mean ± SD or mean ± SEM were included. All studies were reviewed independently following the PRISMA checklist. In cases where there was disagreement over the inclusion of a study, the final decision was made through consensus. For different studies using the same dataset, the most complete study was included. If there was more than 1 fish-oil intervention group, each group was considered as a separate study in the analysis.

Exclusion criteria.

Publications including protocols, letters to the editor, comments, reviews, animal studies, and ecological studies were not included. Moreover, studies without random allocation were not eligible for inclusion. Studies that did not use the PANSS, GAF, BPRS, or report final scores were also not included. Finally, we excluded trials on patients with depression or serious physical illnesses.

The studies by Pawełczyk et al. (36) and McGorry et al. (37) were excluded because they were protocol studies. Studies by Tessier et al. (38), Solberg et al. (39), Evans et al. (40), Sumiyoshi et al. (41), and Assies et al. (42) were excluded for being case-control studies. We also omitted the studies by van der Burg et al. (43), Shakeri et al. (44), Fristad et al. (45), Bošković et al. (30), and Pawełczyk et al. (46) because they did not have the outcomes of interest. The studies by Pawełczyk et al. (47), Arvindakshan et al. (24), and Bentsen et al. (29) did not report final scores in either group, baseline and final scores in the control group, and final SDs, respectively. The studies by Emsley et al. (26), Peet et al. (48), and Sivrioglu

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Abbreviations used: BDNF, brain-derived neurotrophic factor; BPRS, Brief Psychiatric Rating Scale; GAF, Global Assessment of Functioning; PANSS, Positive and Negative Syndrome Scale; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; WMD, weighted mean difference.

TABLE 1 Characteristics of randomized trials included in the systematic review on the effects of fish-oil consumption on psychological function outcomes in psychosis[1]

Study	Reference	Subjects and sex, *n*	Age mean or range,[2] y	Design	Intervention type		Exposure assessment method	Duration, wk	Outcomes	Intervention changes[2], score	Control changes, score[2]	Other interventions	Notes about subjects	Adjustment or matching
					Intervention (name and composition)	Control (name and composition)								
Tang et al.	(57)	Intervention: 40 Males: 24 Females: 16 Placebo: 40 Males: 26 Females: 14	Intervention: 28.00 ± 3.10 Placebo: 28.75 ± 4.70	Randomized placebo-controlled trial	ω-3 FAs 720 mg/d (360 mg/d EPA+ 240 mg/d DHA)	Placebo (100 mg/d Vit E and glycerin and corn oil)	NR	12	PANSS	−0.46 ± 6.89	0.63 ± 7.31	Olanzapine	MetS	Gender, age, olanzapine
Qiao et al.	(58)	Intervention: 32 Males: 21 Females: 11 Placebo: 35 Males: 14 Females: 21	Intervention: 34.09 ± 11.01 Placebo: 34.03 ± 10.38	Double-blind placebo-controlled trial	Fish oil 900 mg/d (540 mg/d EPA+ 360 mg/d DHA)	Placebo (10 mg/d Vit E)	Gas chromatography-MS	8	PANSS	−24.15 ± 16.64	−28.49 ± 16.77	Antipsychotic medication	NR	Gender
Robinson et al.	(55)	Intervention: 25 Placebo: 25	NR	Randomized placebo -controlled trial	ω-3 FAs, 570 mg/d	Soybean/corn blend, 2 capsules	NR	16	BPRS	−17.71 ± 1.69	−13.48 ± 1.87	NR	NR	Lorazepam
Qiao et al.	(59)	Intervention: 28 Males: 17 Females: 11 Placebo: 22 Males: 13 Females: 9	31.98 ± 10.16	Double-blind supplementation trial	ω-3 FAs, 900 mg/d	Vit E 10 mg/d	NR	12	PANSS	−26.1 ± 18.92	−26.77 ± 15.87	NR	Inpatient	No
Jamilian et al.	(32)	Intervention: 30 Males: 16 Females: 14 Placebo: 30 Males: 15 Females: 15	Intervention: 32.01 ± 7.13 Placebo: 31.01 ± 8.81	Triple-blind placebo-controlled clinical trial	ω-3 FAs, 1000 mg/d	Placebo	NR	8	PANSS	−47 ± 8.33	−45.83 ± 4.04	NR	NR	No
Pawełczyk et al.	(60)	Intervention: 36 Males: 19 Females: 17 Placebo: 35 Males: 23 Females: 12	Intervention: 23.2 ± 4.8 Placebo: 23.3 ± 4.8	Randomized, double-blind, placebo-controlled	Fish oil 2.2 g/d (1.32 g/d EPA + 0.88 g/d DHA)	Olive oil + 0.2% Vit E	Polish FFQ	26	PANSS GAF	19.27 ± 1.38 17.22 ± 1.3	−14.42 ± 1.4 12.4 ± 1.32	NR	Inpatient	No
Fenton et al.	(31)	Intervention: 43 Placebo: 44	40 ± 10	Double-blind, placebo-controlled trial	ω-3 FAs, 3000 mg/d	Vit E 24 mg/d + mineral oil	Gas chromatography	16	PANSS	−5 ± 16	−6 ± 18	NR	NR	No

(*Continued*)

TABLE 1 (*Continued*)

Study	Reference	Subjects and sex, *n*	Age mean or range,[2] y	Design	Intervention type		Exposure assessment method	Duration, wk	Outcomes	Intervention changes[2], score	Control changes, score[2]	Other interventions	Notes about subjects	Adjustment or matching
					Intervention (name and composition)	Control (name and composition)								
Peet et al.	(61)	Intervention: 15 Placebo:14	Intervention: 44.2 ± 11.3 Placebo: 43.8 ± 10.8	Double-blind, placebo-controlled trial	EPA 2 g/d	Corn-oil placebo	NR	12	PANSS	−14.4 ± 12.56	−10.3 ± 18.42	Antipsychotic drugs	NR	No
Peet et al.	(61)	Intervention: 16 Placebo: 14	Intervention: 42 ± 10.6 Placebo: 43.8 ± 10.8	Double-blind, placebo-controlled trial	DHA 2 g/d	Corn-oil placebo	NR	12	PANSS	−8.1 ± 18.47	−10.3 ± 18.42	Antipsychotic drugs	NR	No
Nelson et al.	(62)	Intervention: 76 Placebo: 76	19.1 ± 4.6	Randomized, double-blind, placebo-controlled trial	ω-3 FAs, 1.4 g/d	Paraffin	NR	48	BPRS	−9.4 ± 10.1	−9.3 ± 10.0	20 Sessions of CBCM	NR	MADRS
McPhilemy et al.	(33)	Intervention:40 Males: 19 Females: 21 Placebo: 40 Males: 20 Females: 20	Intervention: 45 ± 13 Placebo: 48 ± 12	Randomized double-blind placebo-controlled trial	ω-3 Fas, 2 g/d (1 g/d EPA + 1 g/d DHA)	Vit D_3 35 μg/d + Vit E 1.89 mg/d	NR	52	GAF	−4.97 ± 10.51	−9.4 ± 10.24	NR	NR	No
Szeszko et al.	(63)	Intervention: 12 Placebo: 13	Intervention: 22.7 ± 5.4 Placebo: 21.3 ± 5.3	Double-blind, placebo-controlled randomized clinical trial	Fish oil 1140 mg/d (740 mg/d EPA + 400 mg/d DHA)	Soybean/corn blend	NR	16	PANSS	−16.6 ± 5.80	−12.2 ± 8.22	Risperidone	NR	No
Adolescents														
Mossaheb et al.	(54)	Intervention: 41 Placebo: 40	13–25	Double-blind, placebo-controlled randomized controlled trial	ω-3 FAs, 1.2 g/d	Placebo	NR	12	PANSS GAF	−16.08 ± 4.83 14.5 ± 4.33	−4.7 ± 4.86 7.16 ± 4.54	NR	NR	No
McGorry et al.	(27)	Intervention: 153 Placebo: 151	Intervention: 19.4 ± 4.8 Placebo: 18.9 ± 4.3	Double-blind, placebo-controlled, randomized clinical trial	ω-3 FAs, 1.4 g (840 mg/d EPA+ 560 mg/d DHA)	Paraffin oil, 0.65 to 0.75 g/d	NR	48	BPRS	−7.8 ± 9.3	−7.8 ± 8.4	20 Sessions of CBCM	NR	No

(*Continued*)

TABLE 1 (*Continued*)

Study	Reference	Subjects and sex, *n*	Age mean or range,[2] y	Design	Intervention type		Exposure assessment method	Duration, wk	Outcomes	Intervention changes[2], score	Control changes, score[2]	Other interventions	Notes about subjects	Adjustment or matching
					Intervention (name and composition)	Control (name and composition)								
Amminger et al.	(65)	Intervention: 40 Males: 14 Females: 26 Placebo: 40 Males: 12 Females: 28	Intervention: 16.90 ± 2.42 Placebo: 16.07 ± 1.68	Double-blind randomized controlled trial	ω-3 FAs, 1400 mg/d (700 mg/d EPA + 480 mg/d DHA)	Coconut oil + Vit E 7.6 mg/d + 1% fish oil	Gas chromatography	12	GAF	−2.36 ± 10.37	−3.21 ± 12.54	9 Psychological sessions	NR	No
Amminger et al.	(18)	Intervention: 8 Placebo: 7	16.2 ± 2.1	Randomized, double-blind, placebo-controlled, intervention trial	Fish oil (1180 mg/d 700 mg/d EPA + 480 mg/d DHA)	Coconut oil + Vit E 7.6 mg/d + 1% fish oil	Gas chromatography	12	PANSS GAF	−21 ± 11.61 17.5 ± 9.41	−0.9 ± 17.65 0.7 ± 13.07	NR	NR	No
Amminger et al.	(25)	Intervention: 41 Males: 14 Females: 27 Placebo: 40 Males: 13 Females: 27	Intervention: 16.8 ± 2.4 Placebo: 16.0 ± 1.7	Randomized, double-blind, placebo-controlled trial	ω-3 FAs, 1.2 g/d (700 mg/d EPA+480 mg/d DHA)	Coconut oil + Vit E 7.6 mg/d + 1% fish oil	Gas chromatography	48	PANSS GAF	−15.7 ± 2.8 17.7 ± 2.3	−4.4 ± 2.8 7.2 ± 2.3	NR	NR	No
Wozniak et al.	(64)	Intervention: 7 Placebo: 7	Intervention: 8.1 ± 1.8 Placebo: 9.0 ± 2.7	Randomized, double-blind, controlled clinical trial	ω-3 FAs, 3000 mg/d	Lactose + muslin + mineral oil, 3000 mg/d	NR	12	BPRS	−15 ± 15.57	−2.3 ± 10.93	NR	NR	No
Wozniak et al.	(64)	Intervention: 10 Placebo: 7	Intervention: 8.2 ± 2.3 Placebo: 9.0 ± 2.7	Randomized, double-blind, controlled clinical trial	ω-3 FAs, 3000 mg/d	Lactose + muslin + mineral oil, 3000 mg/d	NR	12	BPRS	−19.6 ± 16.97	−2.3 ± 10.93	NR	NR	No

[1] BPRS, Brief Psychiatric Rating Scale; CBCM, Cognitive-Behavioral Case Management; FA, fatty acid; GAF, Global Assessment of Functioning; MADRS, Montgomery–Åsberg Depression Rating Scale; MetS, metabolic syndrome; NR, not reported; PANSS, Positive and Negative Syndrome Scale; Vit, vitamin.
[2] Values are means ± SDs.

TABLE 2 Study quality and risk-of-bias assessment according to the Cochrane Collaboration's tool on the effects of fish-oil consumption on psychological function outcomes in psychosis[1]

First author (year)	Reference	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting	Other sources of bias	Overall quality
Fenton (2001)	(31)	U	L	L	U	L	L	L	Fair
Peet (2001)	(61)	L	L	H	H	L	L	L	Poor
Amminger (2010)	(25)	L	L	L	L	L	L	L	Good
Amminger (2013)	(18)	U	L	L	L	L	L	L	Good
Mossaheb (2013)	(54)	L	L	L	L	L	L	L	Good
Jamilian (2014)	(32)	L	U	L	L	U	L	L	Fair
Amminger (2015)	(65)	L	L	L	L	L	L	L	Good
Wozniak (2015)	(64)	U	U	L	L	L	L	L	Fair
Pawełczyk (2016)	(60)	L	L	L	L	L	L	L	Good
McGorry (2017)	(27)	L	L	L	L	L	L	L	Good
Nelson (2018)	(62)	L	L	L	L	L	L	L	Good
Qiao (2018)	(59)	U	U	L	L	L	L	L	Fair
Robinson (2019)	(55)	L	L	L	L	L	L	L	Good
Tang (2020)	(57)	L	U	L	L	L	L	L	Good
Qiao (2020)	(58)	L	L	L	L	L	L	L	Good
McPhilemy (2021)	(33)	L	L	L	L	L	L	L	Good
Szeszko (2021)	(63)	L	L	L	L	L	L	L	Good

[1] H, high risk of bias; L, low risk of bias; U, unclear risk of bias.

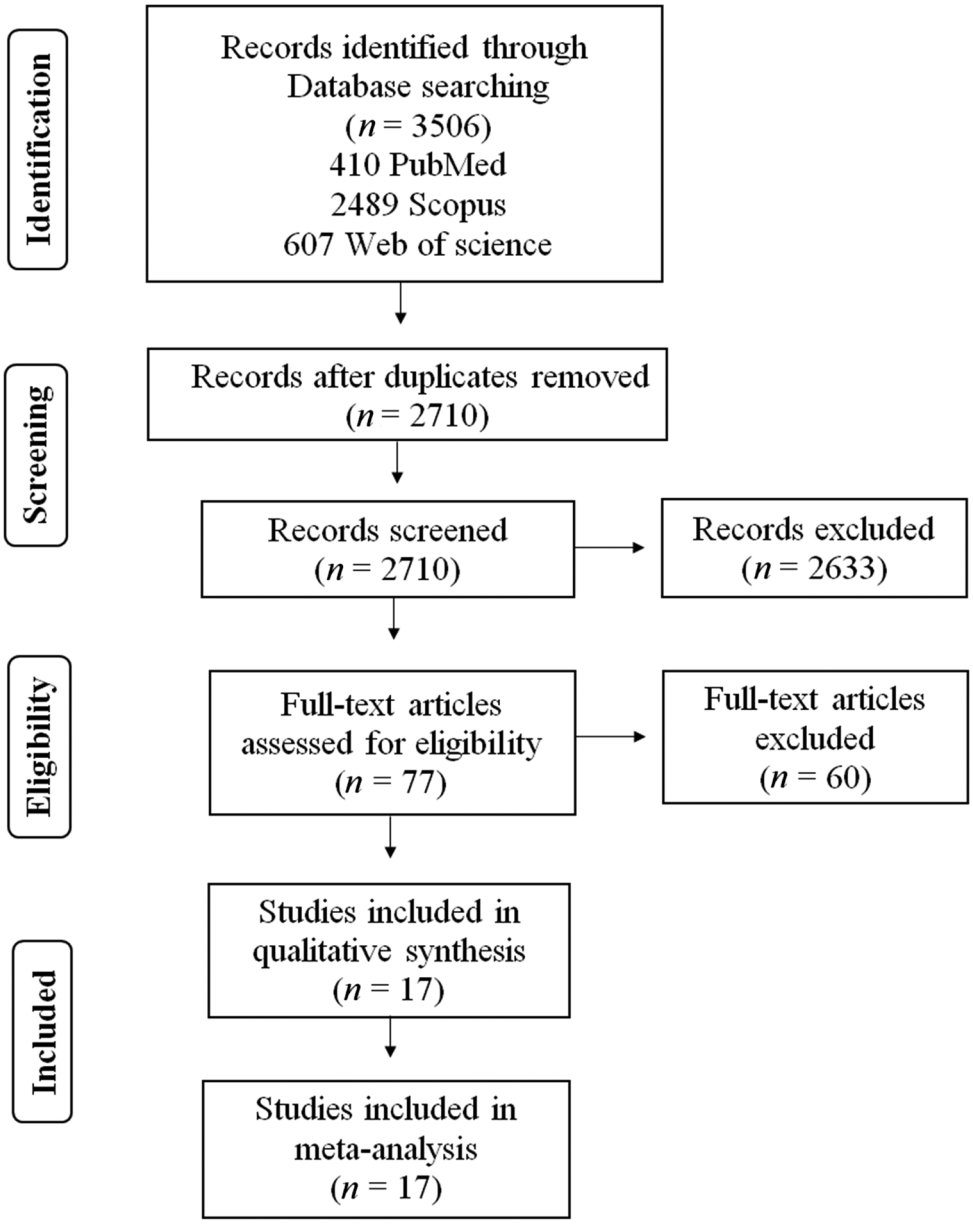

FIGURE 1 PRISMA flow diagram of the systematic search on the effects of fish-oil consumption on psychological function outcomes in psychosis. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

et al. (49) were excluded because they did not present SDs. Despite efforts to communicate with the authors via e-mail, access to the full text of a small number of studies was not possible (50–53). After these exclusions, 17 publications were eligible for inclusion. The study selection process for the systematic review and meta-analysis is illustrated in **Figure 1**.

Data extraction

Databases were assessed and information was extracted and cross-checked by 2 independent reviewers (MM and SE-K). Relevant publications were included after checking the title and abstract. Disagreements between reviewers were resolved through consultation and by reaching consensus with a third reviewer (LA). In this study, the quantity of fish oil was considered as an exposure variable and psychological functioning scores related to psychosis as outcome variables. The following information was extracted after article selection: mean and SD and mean and SE of psychological functioning scores of both groups before and after the intervention as well as mean changes (SD) after the intervention. We obtained the first author's last name, publication year, name of the country in which the study was conducted, age range of participants, gender, study sample size, duration of intervention, health condition, number of participants in each group, study design, and adjustments.

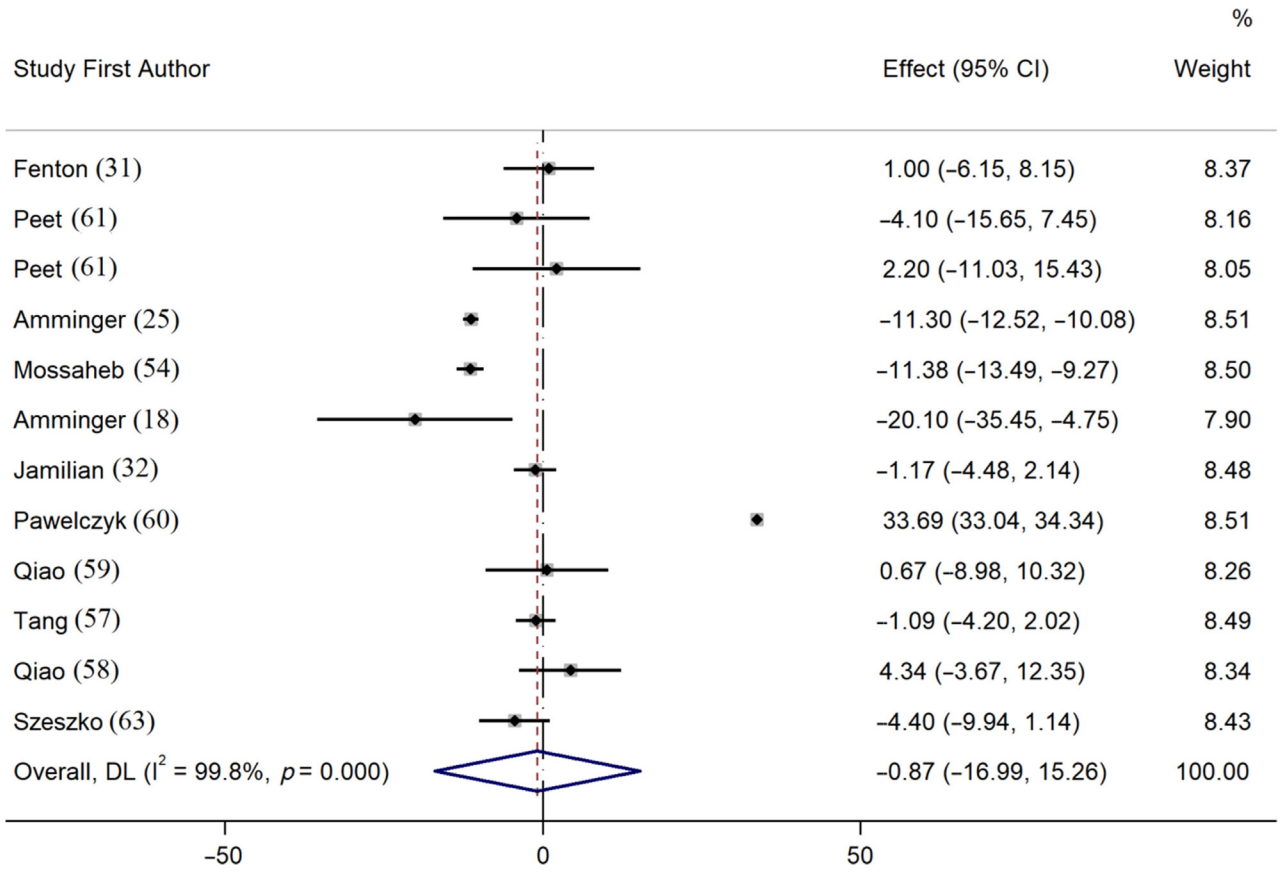

FIGURE 2 Forest plot of the effects of fish-oil consumption on PANSS scores in psychosis. Note: Weights are from a random-effects model. DL, Dersimonian and Laird; PANSS, Positive and Negative Syndrome Scale.

In studies where the values were reported as SEs, the values were converted to SDs. In order to calculate SD changes, we used a regression coefficient of 0.5. In studies by Amminger et al. (25), McPhilemy et al. (33), Mossaheb et al. (54), and Robinson et al. (55), where the values were reported as 2-dimensional bar plot figures, we obtained PANSS, BPRS, and GAF scores using an online Web Plot Digitizer version 4.5 (Ankit Rohatgi). Web Plot Digitizer is a web-based tool designed to extract data from a variety of plots, such as XY coordinates from time-series data. The validity and reliability of this tool for extracting graphed data have already been established. Initial information from each study was further examined in order to ensure that a study was not duplicated.

Quality assessment

To assess the quality of the selected articles, we applied the Cochrane Collaboration's risk-of-bias tool criteria for clinical trials (56). Based on Cochrane's recommendations for clinical trials, the studies were divided into 3 categories based on quality: high risk of bias, moderate risk of bias, and unclear. Two reviewers (MM and SE-K) evaluated bias with respect to adequacy of sequence generation, concealment of the randomization allocation, participant and personnel blinding, outcome assessment blinding, incomplete data, selective reporting, and other possible sources of bias.

Statistical analysis

To analyze the data, random-effect models were performed using restricted maximum likelihood methods. Heterogeneity between studies was estimated based on the I^2 index and high heterogeneity was defined as $I^2 > 50\%$. To estimate the effect size, changes in fish-oil and placebo groups from relevant studies were analyzed using PANSS, BPRS, and GAF as outcomes. Mean differences and SDs were used. Also, data that were reported in figures were transformed to numerical values using Graph Digitizer software. Weighted mean differences (WMDs) and 95% CIs were used to indicate effect sizes. To identify potential sources of heterogeneity, we conducted subgroup analyses. Subgroup analyses were used to report the effect size according to population status, having comorbidities, intervention type, age, other interventions, dose category, type of placebo, duration, and adjustment for PANSS. For GAF, we reported effect size based on population status, type of intervention, age, other interventions, and dose category. Subgroup analyses were also performed for BPRS to report effect sizes based on study population, comorbidities, type of intervention, other interventions, dose

TABLE 3 Pooled estimates of the effects of fish-oil consumption on psychological function outcomes in psychosis on different subgroups[1]

Group	Comparisons, *n*	WMD (95% CI)	*P*[2]	I^2, %	*P*-heterogeneity[3]
Subgroup analysis for the effects of fish-oil consumption on PANSS					
Total	12	−0.87 (−16.99, 15.26)	0.92	99.8	< 0.001
Population status					
Schizophrenia	8	4.57 (−12.13, 21.26)	0.59	99.3	<0.001
Schizoaffective disorder	1	−20.10 (−35.45, −4.75)	0.01	—	—
Psychosis	3	−10.41 (−12.74, −8.07)	<0.001	65.4	0.06
Comorbidity					
No	11	−0.85 (−18.17, 16.46)	0.92	99.8	<0.001
Yes	1	−1.09 (−4.20, 2.02)	0.49	—	—
Age					
≤30 y	6	−2.23 (−25.97, 21.51)	0.85	99.9	<0.001
>30 y	6	−0.20 (−2.78, 2.38)	0.88	0.00	0.81
Other interventions					
No	10	−4.63 (−8.62, −0.65)	0.02	89.7	<0.001
Yes	2	17.55 (−14.49, 49.58)	0.28	98.7	<0.001
Type of placebo					
Paraffin	1	−11.38 (−13.49, −9.27)	<0.001	—	—
Oil	3	−3.53 (−8.20, 1.15)	0.14	0.00	0.66
Vitamin E	2	2.84 (−3.32, 9.01)	0.37	0.00	0.57
Other complex	6	0.40 (−23.15, 23.95)	0.97	99.9	<0.001
Duration					
≤3 mo	8	−3.37 (−8.66, 1.91)	0.21	87.4	<0.001
>3 mo	4	4.78 (−25.77, 35.33)	0.76	99.9	<0.001
Adjustment					
Yes	2	0.32 (−4.35, 4.99)	0.89	34.8	0.22
No	10	−1.38 (−19.64, 16.89)	0.88	99.8	<0.001
Quality					
Good	7	−1.29 (−23.15, 20.56)	0.91	99.9	<0.001
Fair	3	−0.66 (−3.53, 2.21)	0.65	0.00	0.83
Poor	2	−1.37 (−10.08, 7.33)	0.76	0.00	0.48
Subgroup analysis for the effects of fish-oil consumption on BPRS					
Total	5	−2.99 (−6.42, 0.44)	0.08	83.3	<0.001
Population status					
Schizoaffective disorder	2	−15.15 (−24.85, −5.45)	0.002	0.00	0.64
Psychosis	3	−1.58 (−4.91, 1.74)	0.35	88.8	<0.001
Other interventions					
No	3	−0.39 (−2.93, 2.14)	0.76	34	0.22
Yes	2	−9.02 (−21.36, 3.32)	0.15	73	0.05
Type of placebo					
Paraffin	2	0.00 (−1.69, 1.69)	1.00	0.00	1.00
Other complex	3	−9.28 (−18.09, −0.48)	0.03	60.3	0.08
Duration					
≤3 mo	2	−15.15 (−24.85, −5.45)	0.002	0.00	0.64
>3 mo	3	−1.58 (−4.91, 1.74)	0.35	88.8	<0.001
Adjustment					
Yes	2	−2.39 (−6.50, 1.70)	0.25	83.7	0.01
No	3	−8.55 (−20.91, 3.81)	0.17	78.3	0.01
Quality					
Good	3	−1.58 (−4.91, 1.74)	0.35	88.8	<0.001
Fair	2	−15.15 (−24.85, −5.45)	0.002	0.00	0.64

(*Continued*)

TABLE 3 (*Continued*)

Group	Comparisons, *n*	WMD (95% CI)	P^2	I^2, %	*P*-heterogeneity[3]
Subgroup analysis for the effects of fish-oil consumption on GAF					
Total	6	6.66 (3.39, 9.93)	<0.001	95	<0.001
Population status					
Schizophrenia	1	4.82 (4.21, 5.43)	<0.001	0.00	<0.001
Schizoaffective disorder	2	9.45 (−2.45, 21.36)	0.12	72.4	0.05
Psychosis	3	7.07 (3.24, 10.90)	<0.001	89.7	<0.001
Age					
≤30 y	3	5.13 (0.06, 10.19)	0.04	68.3	0.04
>30 y	3	8.10 (5.03, 11.16)	<0.001	83.7	0.002
Other interventions					
No	4	7.83 (4.15, 11.51)	<0.001	85.6	<0.001
Yes	2	4.81 (4.20, 5.42)	<0.001	0.00	0.88
Duration					
≤3 mo	3	6.67 (0.49, 12.85)	0.03	75.7	0.01
>3 mo	3	6.81 (2.12, 11.49)	0.004	97.8	<0.001

[1] BPRS, Brief Psychiatric Rating Scale; GAF, Global Assessment of Functioning; PANSS, Positive and Negative Syndrome Scale; WMD, weighted mean difference.
[2] *P* values for within-subgroup heterogeneity.
[3] *P* values for between-subgroup heterogeneity.

category, placebo type, duration, adjustment, and study quality. A sensitivity analysis was performed to examine the impact of removing any single study on the effect size. To identify small study effects, Begg's adjusted rank correlation and Egger's regression asymmetry tests were conducted. Moreover, publication bias was examined by visual inspection of funnel plots. In the case that publication bias was observed, trim-and-fill analyses were performed to simulate a new effect size by imputing new hypothetical studies in order to correct for publication bias. Dose–response analysis was done considering duration and study population. Data extraction was performed using Microsoft Excel 2016 and data were imported from Excel into Stata 16.0 (StataCorp). All of the statistical analyses, including meta-analyses, were conducted using the special commands for clinical trials in Stata 16.0. $P < 0.05$ was considered as the level of statistical significance.

Results

Findings from the systematic review

Study selection.

We obtained 3506 articles in the initial electronic database search, of which 796 were duplicates. After removing duplicate articles, 2710 unique studies were screened, of which 2633 articles were excluded. Based on the titles and abstracts, 77 were reviewed and their full texts assessed. Finally, 17 articles (18, 25, 27, 31–33, 54, 55, 57–65) met the inclusion criteria and were entered into the systematic review (Figure 1).

Study characteristics.

In total, 1390 participants were included. All studies were published between 2001 and 2021. They all included both men and women. All 17 studies were parallel clinical trials. The total number of articles eligible for inclusion were as follows: 11 studies for PANSS (18, 25, 31, 32, 54, 57–61, 63), 6 studies for GAF (18, 25, 33, 57, 60, 65), and 4 studies for BPRS (27, 55, 62, 64). The main features of the 17 studies that examined the effects of oral intake of fish oil on the psychological functioning scores of PANSS, GAF, and BPRS are shown in **Table 1**. Seven studies were performed in patients with schizophrenia (31, 32, 57–61), 3 studies in patients with schizoaffective disorder (18, 33, 64), and 7 studies in people with other forms of psychosis (25, 27, 54, 55, 62, 63, 65). Except for 1 study (57), the participants had only psychosis and no comorbidities. Participants were, on average, under 30 y old in 11 studies (18, 25, 27, 54, 55, 57, 60, 62–65) and were over 30 y old in 6 studies (31–33, 58, 59, 61). Five studies had more than 1 type of intervention (e.g., fish oil and vitamin supplementation). The dose of fish oil in the intervention group ranged from 570 to 3000 mg/d. In 12 studies (18, 25, 31, 33, 54, 57, 60–65), more than 1000 mg fish oil/d was administered. The placebo was paraffin in 3 studies (27, 54, 62), oil in 2 studies (61, 63), vitamin E in 2 studies (58, 59), and other compounds in 10 studies (18, 25, 31–33, 55, 57, 60, 64, 65). The duration of the intervention ranged from 8 wk to 52 wk. With the exception of 4 studies [Tang et al. (57), Qiao et al. (58), Robinson et al. (55), Nelson et al. (62)], the other clinical trials made no adjustments in the statistical analysis. Adjustments included age, sex, dose and duration of olanzapine and lorazepam, and the Montgomery-Åsberg Depression Rating Scale (MADRS).

Risk-of-bias assessment.

The results of quality assessment according to Cochrane Collaboration's risk-of-bias tool are presented in **Table 2**. The quality assessment revealed that 12 studies were of good quality (18, 25, 27, 33, 54, 55, 57, 58, 60, 62, 63,

65), 4 studies were of fair quality (31, 32, 59, 64), and 1 study was of poor quality (61). Bias was evaluated based on adequate sequence generation, allocation concealment, participant and personnel blinding, outcome assessment blinding, incomplete data, selective reporting, as well as on other possible sources of bias.

Findings from meta-analysis

Effects of fish oil on PANSS.

After analyzing the findings of 11 studies with 12 effect sizes, no significant change in PANSS was observed after oral fish-oil intake (WMD: −0.87; 95% CI: −16.99, 15.26; $P = 0.92$) (**Figure 2**). Significant heterogeneity was found between studies ($I^2 = 99.8\%$, $P < 0.001$). Based on the findings from subgroup analyses, population status, comorbidity, age, other interventions, dose category, type of placebo, study duration, adjustment, and quality were detected as potential sources of heterogeneity (**Table 3**). The subgroup analysis revealed a significant reduction in PANSS following fish-oil supplementation in participants with schizoaffective disorder (WMD: −20.10; 95% CI: −35.45, −4.75; $P = 0.01$). This decrease was also observed in people with psychosis (WMD: −10.41; 95% CI: −12.74, −8.07; $P < 0.001$). No significant increase in PANSS score was observed in any of the subgroups. Except for the removal of the study by Pawełczyk et al. (60) (WMD: −0.75; 95% CI: −1.44, −0.05), the sensitivity analysis showed that results did not change significantly when studies were removed one at a time (WMD: 0.08; 95% CI: −0.85, 1.02). Significant publication bias was observed based on results of Begg's test ($P = 0.05$). However, Egger's test revealed no significant publication bias (95% CI: −31.02, 4.19; $P = 0.12$).

Following a nonlinear dose–response analysis, a significant inverse association was observed between <10 wk of fish-oil supplementation and PANSS (WMD: −10; *P*-nonlinearity = 0.02) (**Supplemental Figure 1**). However, the association between fish-oil dosage and PANSS was nonsignificant (*P*-nonlinearity > 0.05) (**Figure 3**).

Effects of fish oil on BPRS.

Analysis of the 4 studies with 5 effect sizes showed a nonsignificant reduction in BPRS after consumption of oral fish oil (WMD: −2.990; 95% CI: −6.42, 0.44; $P = 0.08$) (**Figure 4**). There was significant heterogeneity between studies ($I^2 = 83.3\%$, $P < 0.001$). Based on the findings from subgroup analyses, population status, dose category, duration, adjustment, and quality were detected as potential sources of heterogeneity. The subgroup analysis showed a significant decrease in BPRS score following fish-oil supplementation in people with schizoaffective disorder (effect size = −15.15, $P = 0.002$). This significant reduction was observed only in studies with fair quality (WMD: −15.16; 95% CI: −24.85, −5.46; $P = 0.002$). None of the subgroups we investigated showed an increase in BPRS score. No individual study had a significant influence on the summary effect in the sensitivity analysis (WMD: −0.81; 95% CI: −1.54, −0.08).

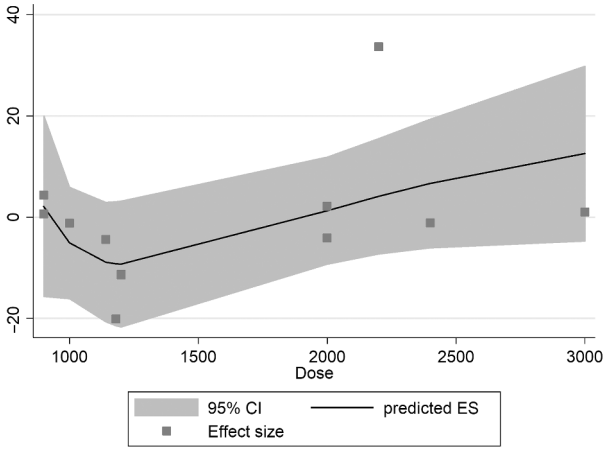

FIGURE 3 Dose–response associations between fish-oil consumption (mg/d) and PANSS scores in psychosis. ES, effect size; PANSS, Positive and Negative Syndrome Scale.

There was no significant publication bias based on the Begg's or Egger's tests ($P = 1.00$) (95% CI: −6.14, 6.01; $P = 0.97$).

The nonlinear dose–response analysis revealed significant inverse associations between dose (>2200 mg/d), duration of fish-oil supplementation (<15 wk), and study population ($n < 50$) with BPRS score (effect size = −8; *P*-nonlinearity = 0.04) (**Figure 5**, **Supplemental Figure 2**).

Effects of fish oil on GAF.

Findings from 6 studies with 6 effect sizes showed significant increases in GAF after oral administration of fish oil (WMD: 6.66; 95% CI: 3.39, 9.93; $P < 0.001$) (**Figure 6**). Although the initial analysis showed a significant increase in GAF score after fish-oil intake, there was significant heterogeneity between studies ($I^2 = 95.0\%$, $P < 0.001$).

Findings from subgroup analyses revealed that population status, age, other interventions, dose, and intervention duration were potential sources of heterogeneity. A significant increase in GAF was observed in all subgroups, except among patients with schizoaffective disorder (WMD: 9.46; 95% CI: −2.45, 21.37; $P = 0.12$). In the sensitivity analysis to investigate the extent of the influence of any 1 study, omitting each study individually showed a significant effect on the pooled WMD of GAF score (WMD: 1.95; 95% CI: 0.62, 3.27). There was no evidence of publication bias ($P = 1.00$, Begg's test; *P*, Egger's test: 0.73; 95% CI: −7.12, 9.31). No significant dose–response associations were observed for intervention dose, intervention duration, or study population with GAF score (*P*-nonlinearity > 0.05) (**Figure 7**) (**Supplemental Figure 3**).

Discussion

This meta-analysis summarized 17 clinical trials on the effects of fish-oil consumption on psychological functioning scores including PANSS, BPRS, and GAF. We found a significant increase in GAF scores following fish-oil consumption. Fish-oil supplementation had no significant

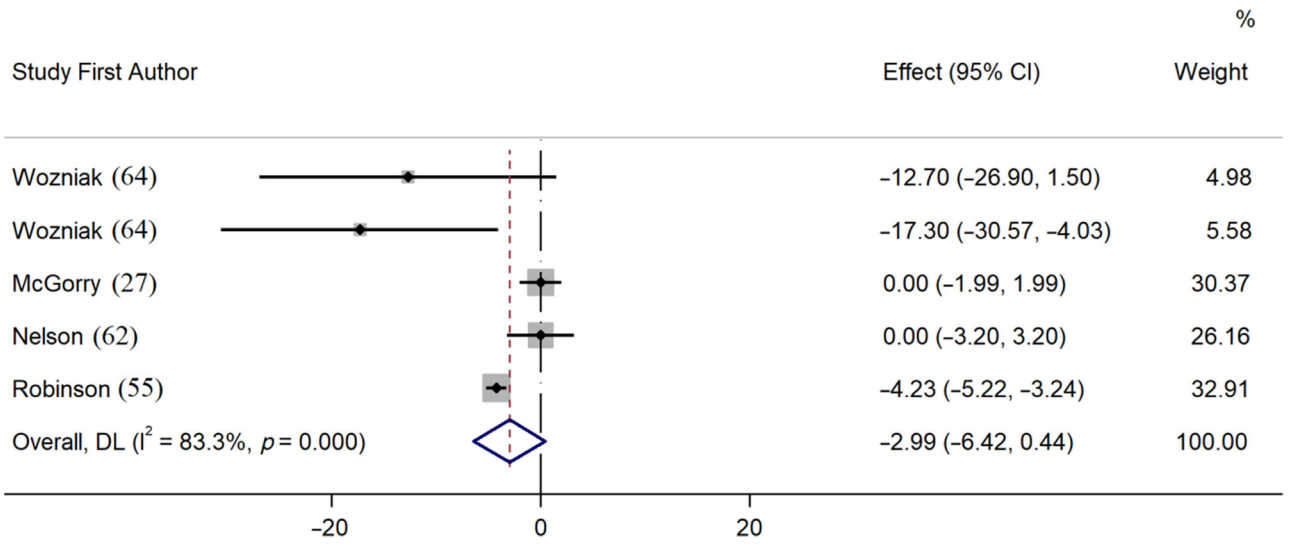

FIGURE 4 Forest plot of the effects of fish-oil consumption on BPRS scores in psychosis. Note: Weights are from a random-effect model. DL, Dersimonian and Laird; BPRS, Brief Psychiatric Rating Scale.

effects on reductions in BPRS and PANSS scores. Intrinsic differences in scores may cause differences in significance. The difference we observed may be due to the fact that the GAF score assesses global occupational, social, and psychological function changes in addition to symptoms (66). It should also be noted that diet and baseline status of ω-3 fatty acids may also have influenced the results of some preliminary studies (17, 67). For instance, people with high fish intake experience fewer pseudo-psychotic symptoms (67). Although the majority of studies included were conducted on fish oil as triacylglycerol and free fatty acids, the intervention study by Fenton et al. (31) used ethyl ester of EPA (E-EPA). It is important to note that ethyl ester derivatives of fish oil are poor substrates for pancreatic lipase and these derivatives of fish oil are less absorbed than triacylglycerol and free fatty acid forms (68, 69).

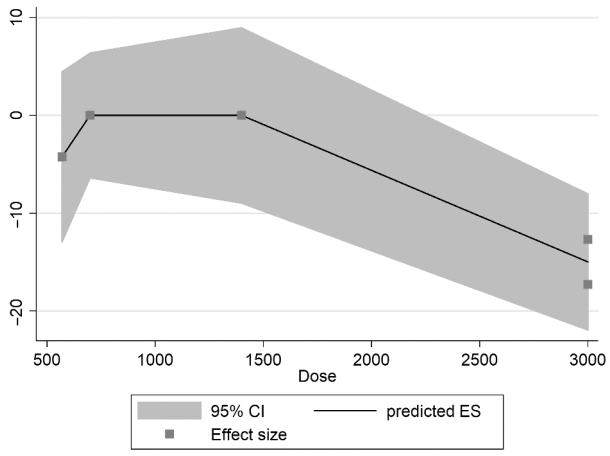

FIGURE 5 Dose–response associations between fish-oil consumption (mg/d) and BPRS scores in psychosis. ES, effect size; BPRS, Brief Psychiatric Rating Scale.

To our knowledge, this is the first meta-analysis examining the effects of oral fish-oil intake on psychological functioning scores of PANSS, BPRS, and GAF in various subgroups. Given that we found significant heterogeneity between studies, subgroup analyses were performed. The subgroup analyses revealed a significant reduction in PANSS scores in the schizoaffective-disorder subgroup as well as in the other-psychotic-disorder subgroup. Inflammation plays a key role in the pathophysiology of schizoaffective disorder. One possible mechanism that ω-3 fatty acids could play in schizoaffective disorder is through ω-3 fatty acids mediating reductions in PANSS by limiting the production of inflammatory prostaglandins and inhibiting the inflammatory processes (70, 71).

Participants with schizoaffective disorder who received shorter interventions (<3 mo) and who participated in studies of fair quality showed greater reductions in BPRS scores. There were significant increases in GAF scores in people with schizophrenia and psychosis among participants >30 y old and with longer interventions (>3 mo).

Our findings from this meta-analysis were consistent with studies that showed no significant reduction in PANSS scores (31, 57–59, 72). However, other studies have shown significant decreases in PANSS scores following fish-oil consumption (26, 29, 32, 48, 54, 61, 73). Reasons for these reductions in PANSS scores could be due to supplementation of marine-derived ω-3 fatty acids instead of fish oil or due to short study durations. After performing linear and nonlinear dose–response analyses, we did not find a significant nonlinear relation between fish-oil dosage and PANSS scores. Furthermore, we did not observe a significant relation between study sample size and PANSS scores. However,

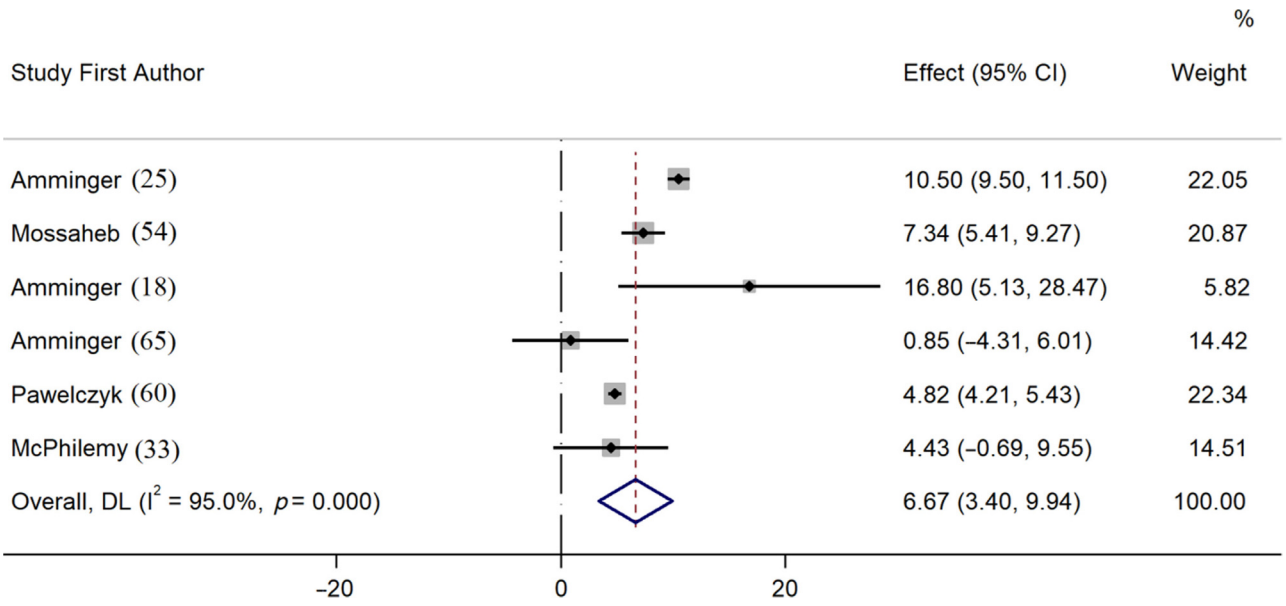

FIGURE 6 Forest plot of the effects of fish-oil consumption on GAF scores in psychosis. Note: Weights are from a random-effect model. DL, Dersimonian and Laird; GAF, Global Assessment of Functioning.

there was a significant decreasing association between fish oil and PANSS scores for supplementation lasting <10 wk.

Our meta-analytic results were in line with some prior clinical trials that did not find significant reductions in BPRS scores (27, 55, 62). Nonetheless, 1 clinical trial and 1 case-control study have reported significant decreases in total BPRS scores after fish-oil supplementation (49, 73). It is possible that the intake of marine-derived ω-3 fatty acids instead of fish oil, short study duration, or small study sample could explain the decreases in BPRS scores observed in these studies. A dose–response analysis indicated that there was a significant nonlinear decreasing correlation between doses of fish oil that were >2200 mg/d and BPRS score. This nonlinear relation showed that a significant reduction in BPRS was observed among studies with sample sizes of <50. We also observed a significant decrease in BPRS scores in interventions lasting <15 wk.

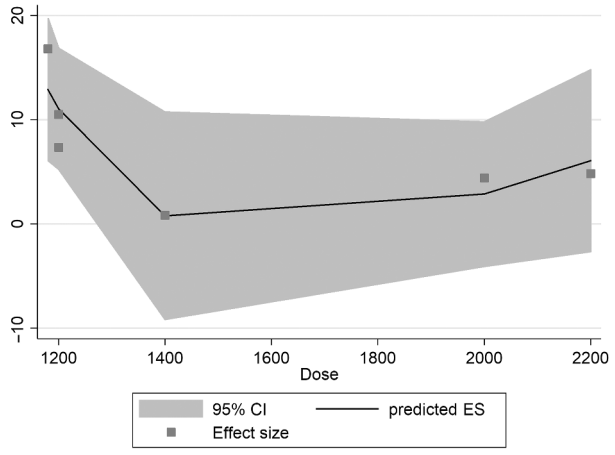

FIGURE 7 Dose–response associations between fish-oil consumption (mg/d) and GAF scores in psychosis. ES, effect size; GAF, Global Assessment of Functioning.

We found significant increases in GAF scores following fish-oil supplementation. This finding agrees with results of several other clinical trials reporting significant improvement in GAF scores following supplementation (18, 25, 54, 60). In contrast, the study by McPhilemy et al. (33) in 2021 showed a nonsignificant decrease ($P = 0.64$) in GAF score following a fish-oil intervention. The latter result could be due to different medications being taken simultaneously, which possibly could counteract the effects of fish-oil supplementation. No significant dose–response relations were found between fish-oil dose and GAF scores (8, 9, 16, 24, 32,). Also, the sample size of the studies did not appear to have a significant effect on GAF scores. Finally, we did not observe any significant nonlinear relations between the intervention duration and the GAF performance scores.

A conclusive mechanism by which ω-3 fatty acids affect mental illness has not yet been determined. Possible mechanisms include the ability of ω-3 fatty acids to reduce inflammatory factors, increasing BDNF and lowering cortisol (8, 9). Finally, ω-3 fatty acids have potential positive effects on cardiovascular factors, which may mediate the relation between ω-3 fatty acids and mental illness (9). Finally, improved DHA status and brain development may be reasons for the improvement in psychological functioning following consumption of ω-3 fatty acids (12).

The main strength of this study is that it is the first meta-analysis to examine the effects of fish oil on the psychological functioning scores using the PANSS, BPRS, and GAF. Hence,

the overall effect is more likely to be accurate than the results of any 1 individual clinical trial. Another study strength is that complete subgroup analyses were performed and dose–response analyses was carried out.

Limitations of this study should also be noted. Despite all efforts to communicate with the authors, some full texts were not available during data extraction (50–53). Furthermore, while changes in PANSS and GAF scores in persons with schizophrenia were observed, we could not find any publications reporting changes in BPRS scores in this population, which indicates the need for further research on the effects of fish oil on BPRS scores in persons with schizophrenia.

In conclusion, fish-oil supplementation was associated with a significant improvement in levels of occupational, psychological, and social functioning in patients with psychosis. This finding may suggest that fish oil could be used as a complementary agent in routine treatment to improve functioning in patients with psychosis. However, more studies with larger study populations, longer duration, and more varied intervention doses are needed to examine the effects of fish-oil consumption on psychological functioning scores in patients with psychosis.

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The authors' responsibilities were as follows—LA, MM, and SE-K: designed the study; MM and SE-K: conducted the literature search and screening of published papers and performed the data extraction and quality assessment, independently; SE-K: performed the statistical analysis; MM and SE-K: interpreted data and wrote the manuscript and PJS contributed to the writing and editing of the manuscript; LA: supervised the study; and all authors: read and approved the final manuscript.

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