



Efficacy of ω -3 supplementation in patients with psoriasis: a meta-analysis of randomized controlled trials

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Received: 5 January 2019 / Revised: 5 January 2019 / Accepted: 25 January 2019 / Published online: 18 February 2019
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Abstract

Several studies have been conducted with the aim of investigating the effect of Omega(ω)-3 on different psoriasis indices including Psoriasis Area and Severity Index (PASI) score, erythema, scaling, itching, area involved, and infiltration. Nevertheless, a pooled analysis of trials that evaluated these variables has not been conducted. Therefore, the aim of this meta-analysis was to assess the efficacy of ω -3 fatty acids in treating patients with psoriasis. We searched through different electronic, references of retrieved articles, and previous related reviews databases up to November 2018. Both combined and stratified analyzes were conducted. A fixed-effects or random effects model was used to assess the mean effect sizes. An eventual 10 studies involving 560 participants were considered as eligible for inclusion in the present meta-analysis. The meta-analysis indicated a significant reduction in PASI score by -1.58 (95% confidence interval (CI), $-2.24, -0.92$; $P < 0.001$) in favor of ω -3 polyunsaturated fatty acid (PUFA) group. The random effects model showed a statistically significant beneficial effect of ω -3 PUFA supplementation on reducing erythema by -1.66 unit and reducing scaling (weighted mean difference (WMD), -0.69 ; 95% CI, $-1.26, -0.13$; $P = 0.02$). Significant improvements in erythema, itching, and scale were observed in the trials which used the higher dosage of ω -3 supplementation. The results of current meta-analysis study support the use of ω -3 PUFA supplementation for the improvement of the evaluated parameters in psoriatic patients. However, well-controlled and randomized studies are needed to confirm the veracity of non-significant and/or equivocal findings.

Keywords Meta-analysis · Polyunsaturated fatty acids · Psoriasis · PUFA

Introduction

Psoriasis is the most common autoimmune and chronic inflammatory, proliferative skin disorder [1–3], while its prevalence is asserted to range from 0.1 to 11.8% in various populations, with an average of 2–3% [3]. Psoriatic lesion involves epidermal keratinocytes and leukocyte cells [2] and is characterized, classically, by sharply demarcated, red indurated plaques over the extensor surfaces of the body and scalp, accompanied by silvery white scales [3, 4]. While there exists a component of heritability to psoriasis susceptibility, the

inflammatory reaction is modulated by diet, lifestyle, and environmental factors, such as infections and stress [1, 2, 5].

Topical medications are the first-line treatment approach prescribed for patients with mild to moderate psoriasis [2, 5]. Typical treatments include various compounds, such as vitamin D analogs, corticosteroids, dithranol, coal tar, and retinoids. However, may confer substantial, negative side effects, including hypercalcemia, skin irritation, cloth staining, teratogenicity, and causes a burning sensation. The second approach includes systemic treatment methods such as cyclosporine and fumaric acid esters, notwithstanding observed side effects, including nephrotoxicity, hypertension, slow onset of action, diarrhea, lymphopenia, bone marrow suppression, nausea, and hepatic fibrosis [1, 2, 5]. Therefore, given the deleterious side effects associated with traditional psoriatic therapies, it is imperative that contemporary, less injurious, treatments be investigated. Polyunsaturated fatty acids (PUFAs) are among such compounds which are showing potential as a safe, adjunctive treatment for many skin disorders, including psoriasis [1–3, 5, 6]. The abnormal keratinocyte

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hyperproliferation in psoriasis arises due to the activation of T cells, which subsequently produces arachidonic acid, leading to the generation of various pro-inflammatory mediators, including prostaglandins, leukotrienes, cytokines, and adhesion molecules via mitogen-activated protein kinase/activator protein-1, extracellular-regulated kinase 1/2, and protein kinase-C activation pathways [1–3, 5]. Omega(ω)-3 fatty acids (i.e., eicosapentaenoic acid (EPA) and docosapentaenoic acid (DHA)) supplementation, in a dose-dependent manner, results in inhibition of various pro-inflammatory mediators and metabolization of EPA and DHA leads to dampening of inflammation and higher resolution of the skin abnormalities [1–3, 5]. These have recently been used alone, or in combination with other drugs, in the treatment of psoriasis [5].

So far, many studies have been conducted with the aim of investigating the effect of ω -3 on psoriasis. For example, an animal study, conducted by Qin et al., to evaluate the effect of omega 3 on psoriasis [6], and asserted ω -3 to elicit mechanistic influence on psoriasis-related inflammation, namely through its downregulation of T helper cells, interleukin (IL)-17, IL-22, IL-23, and stimulation of regulatory T cells [6]. Furthermore, in recent years, many randomized controlled trials have been performed on the efficacy and mechanism of action of ω -3 PUFAs on psoriasis. For example, Upala et al. [5] conducted a systematic review of the effects of n-3 PUFAs on psoriasis and although some studies found that n-3 PUFAs were associated with improvements in the clinical psoriasis area and severity index (PASI) score, erythema, scaling, itching, area involved, and infiltration; numerous studies did not find any reduction in scaling, erythema, area involved, or thickness in the treatment group [5]. Therefore, given the potential to aid clinical treatment, yet equivocal nature of findings in the literature, the aim of this meta-analysis was to assess the efficacy of ω -3 fatty acids, as a monotherapy, in treating patients with psoriasis.

Methods and materials

Search strategy

The present systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [7]. We searched through different databases including ISI web of science, Pubmed/Medline™, Scopus™, EMBASE, and Cochrane library™ up to November 2018 using the following Medical Subject Headings (MeSH) and non-MeSH terms in titles and abstracts: (“fish oil” OR “omega 3” OR “ ω -3” OR “EPA” OR “DHA” OR “fatty acid”) AND (“psoriasis”). Moreover, references of retrieved articles and previous related reviews were also examined to find eligible studies.

Study selection

All published studies were included for meta-analysis if they met the following criteria: (1) Randomized controlled clinical trials with designation of either parallel or cross-over comparing ω -3 PUFA treatment with placebo treatment in patients with psoriasis, (2) providing adequate information upon the baseline and endpoint scores of one of the psoriasis indices, including PASI score (as a tool for measuring the severity and extent of psoriasis by assessing the intensity and affected areas in the head and neck, upper limbs, trunk, and lower limbs), percent total body surface area affected (%TBSA), and subjective reports of disease progression (e.g., erythema, itching, scaling, infiltration, and desquamation), with standard error of the mean (SEM), standard deviation (SD), or 95% CI for intervention and control groups, (3) the study utilized a controlled design, where the difference between the intervention and control group was ω -3 PUFA supplementation, and (4) Studies were published in Persian or English languages. We considered the following criteria as the exclusion criteria: (1) non-human studies, (2) lack of a control group for ω -3 supplementation, (3) non-original or non-randomized controlled trials (RCT) studies including cohort, case-control, or cross-sectional, reviews, letters, case reports, and commentaries.

Quality assessment

The quality of studies were estimated using the Jadad score which includes the following items: (1) randomization (one point for stating random allocation and additional point for describing the method appropriately), (2) blinding (one point for stating that the trial was blinded and additional point for describing the blinding method appropriately; one point was withdrawn if the method of randomization/blinding was inappropriate), and (3) reporting of number and reasons of withdrawals (one point for reporting of number, reasons, and fate of dropouts). The possible score varies between 0 and 5, in which a score of ≥ 3 indicated higher quality studies and a score of less than 3 is considered as the low-quality study [8].

Data extraction

The titles and abstract of included studies were reviewed independently by two authors (MN) and (MT). Differing decisions were resolved by consulting a third reviewer (SJ). We retrieved the full-text papers for those that were potentially relevant to the subject of our study in the initial screening. The data extracted from the included trials were as follows: year of study, study design, location of conducted trial, sample size of intervention/control groups, participant characteristics (gender and age), duration of follow up, clinical condition of participants, dosage of intervention supplementation, and reported significant outcomes.

If the papers contained inadequate details, we planned to contact the authors to obtain the missing information. Where this was unsuccessful, we planned to calculate the missing data from the raw numbers and *P* values reported.

Statistical analysis

Variable effects were defined as the weighted mean difference (WMD) with 95% confidence interval (CI) and the corresponding standard deviation (SD) in any of the psoriasis indices values. In case of not reporting the SD values, we calculated the SD from standard errors, *P* values, 95% CIs, or by converting the median and interquartile range to mean, and SE using available formulas. We assessed the I^2 index and χ^2 test on Cochrane's *Q* statistic to quantify the extent of heterogeneity, in which $P < 0.05$ or $I^2 > 50\%$ was defined as heterogeneous. A random effects model was used to pool the effect size if significant heterogeneity was indicated between studies. Otherwise, a fixed-effects model was used. We used funnel plots, Begg's rank correlation test, and Egger's weighted regression test to examine any potential publication biases. To identify any potential heterogeneity source, we conducted sensitivity, stratified, and meta-regression analyses in accordance with the Cochrane guidelines [9].

All analyses were performed in Review Manager Software (Review Manager 5.3; Cochrane Collaboration, Oxford, England) and comprehensive meta-analysis (version 3.2; Biostat). A *P* value of less than 0.05 was considered as statistically significant.

Results

Literature search and selection of studies

The flow diagram of study selection is shown in Fig. 1. A total number of 87 studies were initially identified after duplicates had been removed. In the next step, 74 more studies were excluded for the following reasons: experimental studies (in vitro or non-human trials) ($n = 61$), non-clinical studies (reviews, editorials, letters, and case reports) ($n = 13$). Therefore, 13 possibly relevant studies were deemed for full text review. After screening, three articles were excluded because they: (1) did not administer ω -3 as the intervention, or administered as a combined supplementation; (2) insufficient reported data of psoriasis indices in the baseline and the end of follow up. An eventual 10 studies involving 560 participants were considered as eligible for inclusion in the present meta-analysis.

Study characteristics and quality assessment

Characteristics of the included studies are presented in Table 1. In total, 10 RCTs [1, 3, 10–17] were included in the meta-analysis, comprising a total of 278 individuals in the intervention group and 282 in the control group. Patients treated in these RCTs had psoriasis [3, 10–17] except for one in which the patients were obese with psoriasis [1]. Nine studies were published in English and the remaining one in Polish [3]. Study duration ranged from 4 to 48 weeks with a median of 8 weeks. The dosage of ω -3 supplementation was between 240 and 3600 mg/day with the median of 1800 mg/day EPA. The studies supplied ω -3 interventions with different forms including EPA [11], EPA and DHA [3, 10, 12–17], and α -linolenic acid (ALA) [1]. All included studies were published between 1988 and 2017 and had been conducted in India ($n = 1$) [3], Spain ($n = 1$) [10], Great Britain ($n = 1$) [11], Norway ($n = 1$) [12], Argentina ($n = 1$) [13], Germany ($n = 1$) [14], Italy ($n = 1$) [1], USA ($n = 2$) [15, 16], and Scotland ($n = 1$) [17]. There were no reports of serious adverse effects and only slight abdominal distress was reported in the reviewed papers.

Table 2 presents the results of the study quality assessment. According to the previous studies, which indicated the studies with Jadad score of more than 3 as high-quality studies. Most included studies (7 of 10 studies) showed higher quality [1, 11, 12, 14–17] and the remaining 3 studies considered as low methodologic quality [3, 10, 13].

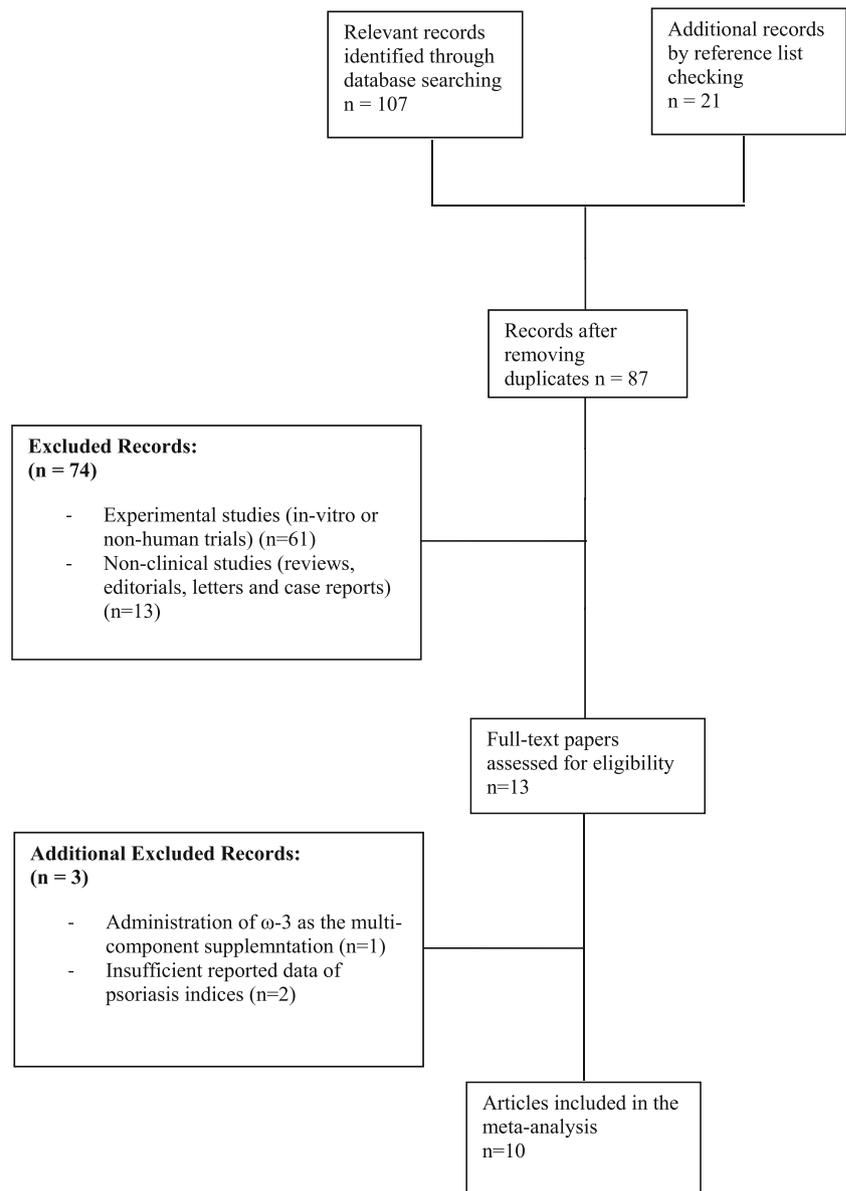
Effect of ω -3 PUFA supplementation on PASI score

Three studies reported data on PASI improvement [1, 3, 10] with no observed heterogeneity among these studies ($P = 0.64$, $I^2 = 0\%$). The meta-analysis of the included trials indicated a significant reduction in PASI score by -1.58 [95% CI, -2.24 , -0.92 ; test for overall effect, $Z = 4.69$ ($P < 0.00001$)] in favor of ω -3 PUFA group with the standardized mean difference (SMD) and 95% CI of -0.56 [-0.83 , -0.28] (Fig. 2 a).

Effect of ω -3 PUFA supplementation on erythema

Eight studies had sufficient data for inclusion in meta-analyses erythema [3, 10–16]. There was significant heterogeneity between these studies ($P < 0.00001$, $I^2 = 99\%$). The random effects model showed a statistically significant beneficial effect of ω -3 PUFA supplementation on reducing erythema by -1.66 unit [(95% CI, -2.52 , -0.81 ; test for overall effect, $Z = 3.82$ ($P = 0.0001$)]. The pooled standardized mean difference (SMD) and 95% CI were -1.55 [-2.47 , -0.62] (Fig. 2 b).

Fig. 1 Flow chart of article selection process



Effect of ω -3 PUFA supplementation on itching

Five studies had sufficient data for inclusion in meta-analyses of itching [1, 11, 13, 16, 17]. Significant heterogeneity among trials was observed for itching ($P < 0.00001$, $I^2 = 94\%$). The random effects model did not indicate any significant pooled WMD favoring ω -3 PUFA supplement versus control for itching [WMD, 0.25; 95% CI, -0.65 , 1.15; test for overall effect, $Z = 0.55$ ($P = 0.58$)] (Fig. 2 c).

Effect of ω -3 PUFA supplementation on %TBSA

Four studies had sufficient data for inclusion in meta-analyses of %TBSA with a significant observed heterogeneity among these studies ($P < 0.00001$, $I^2 = 99\%$) [3, 11, 12, 15]. The

random effects model did not show a significant pooled WMD favoring ω -3 PUFA supplement versus control for %TBSA [WMD, -7.40 ; 95% CI, -16.75 , 1.95; test for overall effect, $Z = 1.55$ ($P = 0.12$)] (Fig. 2 d).

Effect of ω -3 PUFA supplementation on scaling

Five studies had sufficient data for inclusion in meta-analyses of scaling [10, 11, 13, 15, 16]. We found a statistically significant heterogeneity among the trials for scaling ($P < 0.00001$, $I^2 = 98\%$). The random effects model revealed a significant pooled WMD for the efficacy of ω -3 PUFA supplementation on reducing scaling [WMD, -0.69 ; 95% CI, 1.26, -0.13 ; test for overall effect, $Z = 2.41$ ($P = 0.02$)] with the pooled SMD of -2.06 [-3.66 , -0.46] (Fig. 2 e).

Table 1 Characteristics of included studies

Author	Year	Country	No. (intervention)	No. of controls	Gender	Age (mean)	Follow-up duration (weeks)	Clinical condition	Intervention (dosage)	Control (dosage)	Significant outcome
Adil	2017	India	95	93	F/M	36.24	12	Psoriasis	1800 mg (EPA-DHA)	Topical paraffin	There was a statistically significant difference in PASI, erythema, in duration, desquamation scores, and area involved between the two groups after 12 weeks. In all the secondary endpoints studied (scalp lesion, lesion of target plaque erythema, infiltration, and scaling) a significant improvement was observed in the group treated the treatment versus the control group.
Balbás	2011	Spain	15	15	F/M	58.97	4	Psoriasis	560–80 mg (EPA-DHA)	Tacalcitol	A significant improvement in itching at 12 weeks. No significant change in the clinical manifestations of psoriasis in either group after 8 weeks of treatment. Significant improvement in erythema and scaling; significant differences between treatments were achieved in scaling but not in erythema.
Bittner	1988	Britain	11	13	F/M	34.9	12	Psoriasis	1800 mg EPA	Olive oil	Moderate improvement in clinical manifestations (changes in score systems between 16 and 25% from the baseline within 10 days). The severity of disease markedly decreased in all patients of the n-3 group, with improvements in all score systems ranging between 45 and 76% within 10 days.
Bjorneboe	1988	Norway	13	14	F/M	40	8	Psoriasis	1800–1200 mg(EPA-DHA)	Olive oil	A significant clinical improvement was observed in patients assuming the low-calorie high n-3 PUFAs diet respect to controls. Specifically Psoriasis Area Score Index.
Escobar	1992	Argentina	25	25	F/M	40.3	4	Psoriasis	EPA-DHA	Liquid paraffin	Patients in the fish oil group had a greater decrease in the total body surface area of psoriasis and more improvement compared with patients in the olive oil group. The improvement in the fish oil group was significantly greater for all parameters compared with the change in the olive oil group.
Grimminger	1993	Germany	9	11	F/M	39.7	2	Psoriasis	2100–21,000 mg(EPA-DHA)	Omega 6	Scaling was reduced from the baseline in treatment group. The fish oil group had less cellular infiltration and had improvement in desquamation and redness. All measures of skin disease activity including severity, percentage body affected, and itch were unchanged.
Guida	2014	Italy	18	18	F/M	52.18	12	Psoriasis/obesity	2600 mg ALA	Cyclosporine	
Gupta	1989	USA	9	11	F/M	51	15	Psoriasis	3600–2400 mg (EPA-DHA)	Olive oil	
Soyland	1993	USA	61	62	F/M	47	16	Psoriasis	510–320 mg (EPA/DHA)	Corn oil	
Veale	1994	Scotland	19	19	F/M	40	36	Psoriasis	240–132 mg (EPA/DHA)	NSAID	

Table 2 Quality of the included studies based on the Jadad scale

Study; year	Blinding	Randomization	Withdrawals and dropouts descriptions	Total score
Adil; 2017	0	0	1	1
Balbas; 2011	0	0	1	1
Bittiner; 1988	1	1	1	3
Bjorneboe; 1988	1	1	1	3
Escobar; 1992	1	1	0	2
Grimminger; 1993	1	1	1	3
Guida; 2014	1	2	1	4
Gupta; 1989	1	1	1	3
Soyland; 1993	1	1	1	3
Veale; 1994	1	1	1	3

Effect of ω -3 PUFA supplementation on desquamation and infiltration

Four and 3 studies had sufficient data for inclusion in meta-analyses of desquamation [3, 12, 14, 16] and infiltration [12, 14, 16], respectively. The observed heterogeneity between studies for both desquamation and infiltration was statistically significant ($P < 0.00001$, $I^2 = 97\%$). The random effects model did not show a significant net change for the efficacy of ω -3 PUFA supplementation on improving desquamation and infiltration [desquamation WMD, -0.33 ; 95% CI, $-1.35, 0.69$; test for overall effect, $Z = 0.64$ ($P = 0.52$); infiltration WMD, -0.31 ; 95% CI, $-0.82, 0.20$; test for overall effect, $Z = 1.19$ ($P = 0.24$)] (Fig. 2 f, g).

Subgroup analyses

The results of subgroup analyses are presented in Table 3. To evaluate the influence of ω -3 PUFA supplementation on the complications of psoriasis, included studies were divided into two distinct subgroups according to the dosage of supplementation (< 1800 vs. ≥ 1800 mg/day) and the duration of study (≤ 8 vs. > 8 weeks). Test of interaction showed significance for the subgroup differences regarding to ω -3 PUFAs' dosage of ≥ 1800 mg/day. Significant improvements in erythema, itching, and scale were observed in the trials which used the higher dosage of ω -3 supplementation with a significant reduction of heterogeneity in the scale index. Although, the lower dosage of ω -3 PUFA supplementation and different duration of studies showed significant improvements in some indices, the between-study heterogeneities are significant and robust (Table 3).

Sensitivity analysis

Influence analysis was performed to examine the effect of each study on the estimated pooled effect size. Results of systematic removal of each study did not influence the

overall weighted mean difference of ω -3 PUFA supplementation on erythema, which ranged from -0.54 (95% CI = $-0.95, -0.13$) to -1.96 (95% CI = $-3.12, -0.80$) (Fig. 3).

Meta regression

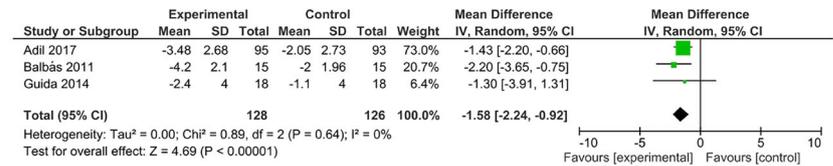
A meta-regression analysis was conducted to investigate the effect of different modulators in determining the heterogeneity of estimates. In accordance with subgroup analysis, higher dosage of ω -3 PUFA supplementation and lower duration of supplementation were significantly associated with the improvement in both erythema (dosage of ω -3 PUFA supplementation slope, -0.0007 ; 95% CI, $-0.0005, -0.0006$; $P < 0.001$, Fig. 4 a-1; duration of supplementation slope, 0.05 ; 95% CI, $0.03, 0.06$; $P < 0.001$, Fig. 4 a-2) and scale complications (dosage of supplementation slope, -0.0004 ; 95% CI, $-0.00053, 0.00032$; $P < 0.001$, Fig. 4 b-1; duration of supplementation slope, 0.05 ; 95% CI, $0.03, 0.07$; $P < 0.001$, Fig. 4 b-2), whereas lower duration of supplementation were not associated with the improvement in PASI score.

Publication bias

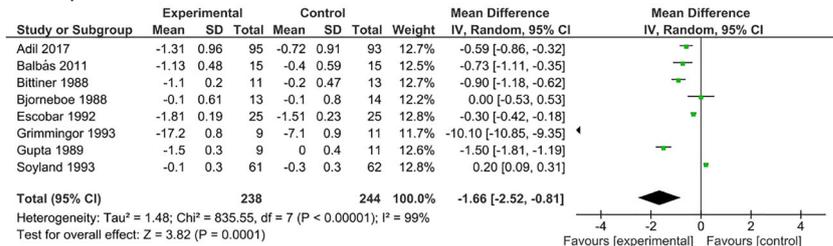
Among the main outcomes, erythema was selected as a representative index for assessing publication bias, as most of the included studies measured erythema as one of the psoriasis complications. Begg's rank correlation (Kendall's Tau with continuity correction, -0.39 ; $Z = 1.36$; two-tailed $P = 0.17$) and Egger's linear regression test (intercept, -12.7 ; standard error, 5.25 ; 95% CI, $-25.6, 0.06$; $t = 2.43$, $df = 6$; two-tailed $P = 0.06$) did not indicate statistically significant publication bias for erythema outcome. This was confirmed according to the symmetric visual inspection of the corresponding funnel plot (Fig. 5).

Fig. 2 Forest plots of analysis of the effect of ω -3 supplementation on psoriasis indices including PASI (a), erythema (b), itching (c), %TBSA (d), scale (e), desquamation (f), and infiltration (g). Random effects model was used to pool the mean change of indicators. CI, confidence interval; I-squared inconsistency; PASI, Psoriasis Area Severity Index; %TBSA, percent total body surface area

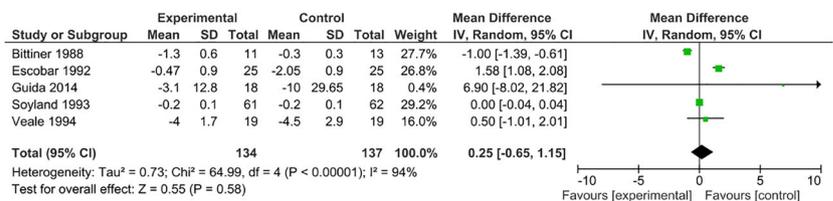
a PASI score



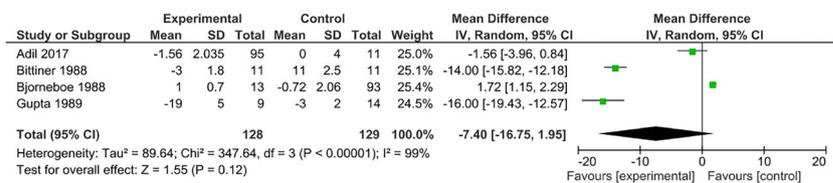
b Erythema



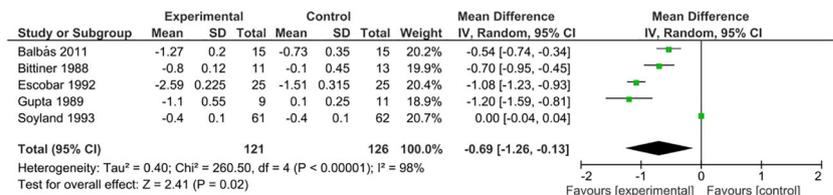
c Itching



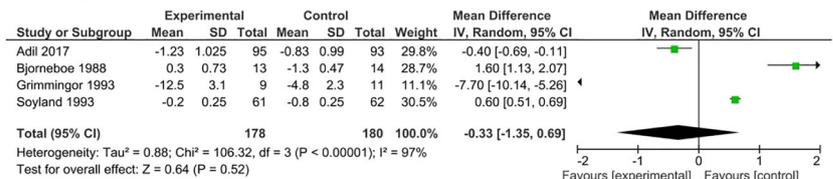
d %TBSA



e Scale



f Desquamation



g Infiltration

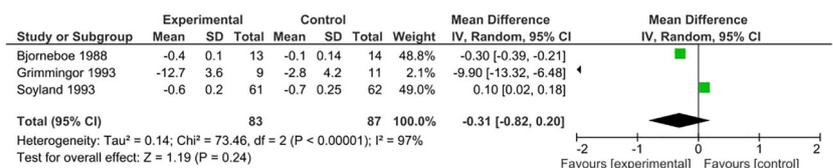


Table 3 Stratified analysis

Subgroup	PASI		Erythema		Itching		Overall effect (P value)	
	WMD (95% CI)	Test for heterogeneity (I^2 , P)	WMD (95% CI)	Overall effect (P value)	WMD (95% CI)	Test for heterogeneity (I^2 , P)		
Dosage < 1800 mg/day	-2.20 [-3.65, -0.75]	Not applicable	-0.25 [-1.16, 0.66]	P=0.60	0.00 [-0.04, 0.04]	0%, P=0.52	P=0.99	
≥ 1800 mg/day	-1.43 [-2.20, -0.66]	Not applicable	-2.18 [-3.51, -0.85]	P=0.001	-1.00 [-1.39, -0.61]	Not applicable	P<0.00001	
Duration ≤ 8 weeks	-2.20 [-3.65, -0.75]	Not applicable	-2.76 [-5.51, -0.01]	P=0.05	1.58 [1.08, 2.08]	Not applicable	P<0.001	
> 8 weeks	-1.42 [-2.16, -0.68]	0%, P=0.93	-0.69 [-1.49, 0.11]	P=0.09	-0.28 [-1.12, 0.57]	89%, P<0.00001	P=0.52	
Subgroup	Desquamation	Infiltration	TBSA	Scale	WMD	Overall effect (P value)	Test for heterogeneity (I^2 , P)	Overall effect (P value)
	WMD (95% CI)	Overall effect (P value)	Test for heterogeneity (I^2 , P)	Overall effect (P value)				
Dosage < 1800 mg/day	0.60 [0.51, 0.69]	0.10 [0.02, 0.18]	0.10 [0.02, 0.18]	Not applicable	Not applicable	Not applicable	Not applicable	P=0.33
≥ 1800 mg/day	-1.53 [-3.73, 0.66]	-4.94 [-14.34, 4.46]	-4.94 [-14.34, 4.46]	P=0.30	-7.40 [-16.75, 1.95]	P=0.12	96%, P<0.00001	P=0.0002
Duration ≤ 8 weeks	-2.97 [-12.08, 6.14]	-4.94 [-14.34, 4.46]	-4.94 [-14.34, 4.46]	P=0.30	Not applicable	Not applicable	99%, P<0.00001	P=0.003
> 8 weeks	0.11 [-0.87, 1.09]	-0.31 [-0.82, 0.20]	-0.31 [-0.82, 0.20]	P=0.24	-7.40 [-16.75, 1.95]	P=0.12	Not applicable	P=0.09
	Test for heterogeneity (I^2 , P)							
	Not applicable							
	98%, P<0.00001	98%, P<0.00001	97%, P<0.00001	97%, P<0.00001	99%, P<0.00001	99%, P<0.00001	96%, P<0.00001	62%, P=0.06
	98%, P<0.00001	98%, P<0.00001	97%, P<0.00001	97%, P<0.00001	99%, P<0.00001	99%, P<0.00001	94%, P<0.00001	97%, P<0.00001
	98%, P<0.00001	98%, P<0.00001	97%, P<0.00001	97%, P<0.00001	99%, P<0.00001	99%, P<0.00001	97%, P<0.00001	97%, P<0.00001

PASI, psoriasis area and severity index; WMD, weighted mean difference; CI, confidence interval; I^2 , percentage score for heterogeneity

Discussion

While animal studies have routinely purported the therapeutic effect of ω -3 fatty acids on psoriasis, human-based studies are much more equivocal in their conclusions. We therefore sought to conduct a meta-analysis to assess the efficacy of ω -3 fatty acids, as a monotherapy, in treating patients with psoriasis. In accord with the aim of this study, our key findings were that ω -3 PUFA supplementation, as a monotherapy, elicited significant reductions in PASI score, erythema, and scaling. Furthermore, our subgroup analysis highlighted that ω -3 supplementation with dosages of > 1800 mg/day and < 8 weeks in duration was associated with more beneficial outcomes.

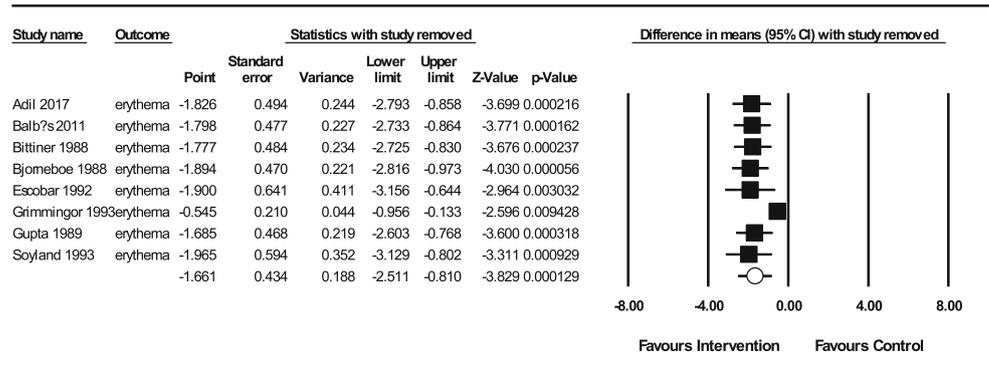
The PASI score is a subjective assessment based on estimation by clinicians. Studies have shown that it can be unreliable due to its complex score calculation, it can be difficult to interpret due to its non-linearity, and the amount of improvement in the score does not always correspond to clinical relevance. Furthermore, the PASI score does not take into account the disproportionate disease burden reflected in the more visible (hands, feet, nails, face) or covered (genitalia and perianal) body regions, or the impact on patient quality of life. Specifically relating to PASI score, three studies reported such data [1, 3, 10]. ω -3 PUFAs, in general, are considered to modify inflammatory and immune reactions; moreover, ω -3 PUFAs have direct effects on reducing body weight and fat deposition via effects on lipid metabolism-related genes [18] offering a conceivable explanation as to why PASI score may be reduced following a period of supplementation. Of importance is what, practically, demarcates a clinically meaningful improvement. Currently, it is reported that for clinically meaningful improvement in psoriatic patients is at least 50–75% improvement, which has been subsequently translated into 50–75% improvement in the PASI score [19]. Notwithstanding the difficulties in interpreting PASI score, this meta-analysis has highlighted the significant improvements manifest through ω -3 PUFA monotherapy, and therefore warrants consideration in prescribed treatment by clinicians.

The levels of arachidonic acid (AA) and its metabolites, particularly leukotriene B4 (LTB4) and 12-hydroxyeicosatetraenoic acid (12-HETE), are higher in psoriatic plaques than in clinically

uninvolved skin [15]. Both LTB4 and 12-HETE are chemotactic for neutrophils, leading to the contemporary use of n-3 PUFAs as an adjunct therapy because their anti-inflammatory and/or anti-chemotactic properties seem to induce a protective effect against cutaneous diseases, including psoriasis [17], which has been avowed in the present meta-analysis. Furthermore, Bitteiner [11] assert that since stable plaque psoriasis improves significantly with PUFA supplementation, more profound effects are likely in the inflammatory unstable variants such as erythrodermic psoriasis. This assertion was supported in eight studies included in this meta-analysis [3, 10–16], yielding a statistically significant beneficial effect of ω -3 PUFA supplementation, reducing erythema by – 1.66 units. Five studies in this meta-analysis [10, 11, 13, 15, 16] reported that ω -3 PUFA supplementation significantly reduced scaling and has been suggested that concomitant reduced inflammatory markers in ω -3 PUFA supplementation groups may be mediating such positive changes. Grimminger et al. [14], for example, measured the level of leukotriene B4 and B5, platelet-activating factor (PAF), and 5-HETE. They reported a sharp increase in the generation of LTB5 and 5-HEPE starting from day 3 to day 10 of n-3 PUFA infusion, indicating the reduction of chemotactic and neutrophil activation.

Of note, while our meta-analyses highlighted significant improvements in a number of variables, supplementation with ω -3 PUFA did not result in any significant improvements in itching, %TBSA, or desquamation and infiltration. The reason for no significant effect manifest in this meta-analysis stems from the starkly contrasting, and equivocal results in the included studies. Recently, and similarly, Upala et al. [5], in their systematic review, noted ω -3 PUFAs were associated with improvements in the PASI score, erythema, scaling, itching, area involved, and infiltration; however, some studies did not find reduction in scaling, erythema, area involved, or thickness in the treatment group. While Upala et al. [5] reported that ω -3 PUFA supplementation may yield promising results, they were unable to conclusively support its’ use to improve psoriasis severity. In contrast, by conducting the present meta-analysis, we were able to robustly pool, weight, and analyze all relevant studies, while controlling for mediators and assessing heterogeneity, thereby permitting more detailed,

Fig. 3 Sensitivity analysis for the effect of ω -3 supplementation on erythema



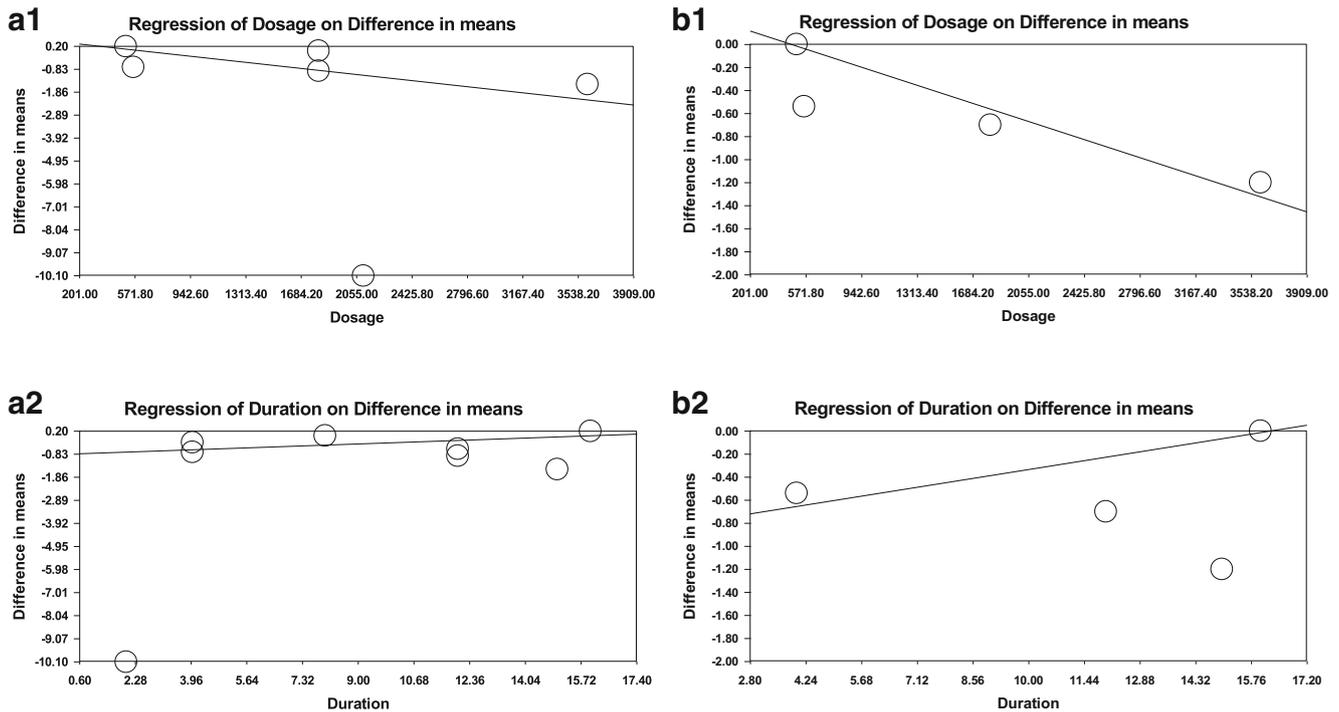


Fig. 4 **a** Meta-regression bubble plots of the association between mean changes in erythema score and (1) dosage of ω -3 supplementation, (2) duration of supplementation. **b** Meta-regression bubble plots of the

association between mean changes in scale score and (1) dosage of ω -3 supplementation, (2) duration of supplementation

quantitative scrutiny of the current evidence base, rather than relying on a qualitative synthesis of individual studies’ mean data. While we have elucidated the current evidence for the effectiveness of ω -3 PUFA supplementation on PASI score, erythema, and scaling; however, it is evident that more well-controlled studies specifically investigating itching, %TBSA, or desquamation and infiltration are needed to facilitate a more definitive conclusion.

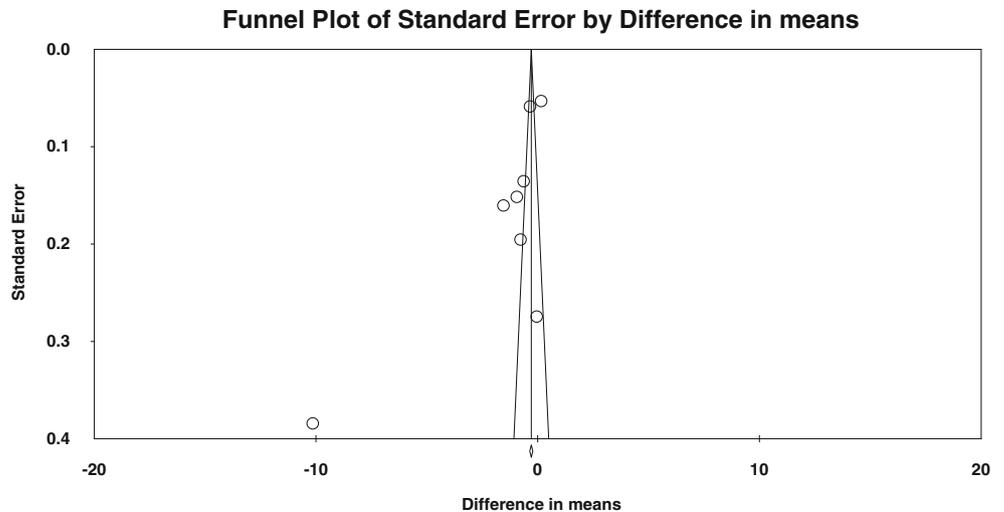
Interestingly, significant improvements in erythema, itching, and scale were observed more readily in the trials which used ω -3 supplementation dosages > 1800 mg/day

(Table 3). This finding necessitates further work to ascertain the optimal dosing of ω -3 for it to confer significant benefits.

Strengths and limitations

The primary strength of this study was that this is the first meta-analysis to assess the impact of ω -3 supplementation on the severity of psoriasis, manifest in human-based RCTs; and given the potential influence on clinical practice, this is a major finding. The evidence base, prior to this meta-analysis, was bereft of uniformity, and urgently required a summative,

Fig. 5 Funnel plot detailing publication biases in all included trials



quantitative assessment, which we have provided. We demonstrated that there is sufficient evidence for ω -3 supplementation to elicit positive effects on PASI score, erythema, and scaling. Another strength of the current meta-analysis is the assimilation of the heterogeneous sample of participants, with a range of demographic status, ethnicities, and ages. We were also able to stratify analyses based on both the duration of supplementation and dosage, giving clinicians foresight into expected outcomes based on such information.

Notwithstanding, the current study has some limitations worth considering. The analyses were not restricted to solitarily include psoriatic arthritis patients; rather, we stipulated that patients need only have some skin involvement, which consequently permitted a large number of studies and participants to be included for analyses. Furthermore, this is the first meta-analysis to assess the impact of ω -3 supplementation on the severity of psoriasis, which permits more nuanced guidance for further study. Indeed, we therefore assert that analyses of psoriatic arthritis patients be investigated, to ascertain the efficaciousness of ω -3 supplementation in this more specific population. A large number of included trials were small in sample size, and it has been asserted by Sterne et al. [20] that it is probable for studies with small sample sizes to report bigger effect sizes in intervention arms than studies with larger participant pools, nevertheless, this was out of the operational control of the meta-analysis. A further limitation of the present study was the paucity of eligible studies, highlighting the need for more, high-quality RCT's. A further potential limitation is the plethora of controlling treatments administered across the included studies, although our meta-analysis showed, for some variables, ω -3 is significantly better vs. control groups, the controls varied from topical paraffin, talcocalcitol, various oils, and medications; conceivably influencing the strength of results found. Therefore, the authors recommend that in addition to further RCTs being conducted, studies should contain at least one standardized control arm.

Conclusion

The results of current meta-analysis study support the use of ω -3 PUFA supplementation, as a monotherapy, for the improvement of PASI score, erythema, and scaling in psoriatic patients, with subgroup analysis highlighting greater improvements with dosages of > 1800 mg/day and < 8 weeks in duration. However, the literature base remains equivocal as to whether significant benefits are incurred for itching, %TBSA, or desquamation and infiltration. Therefore, notwithstanding the positive effect elicited by ω -3 PUFA supplementation for some clinically relevant variables, it is evident that more, well-controlled and randomized studies are needed to confirm the veracity of non-significant and/or equivocal findings.

Compliance with ethical standards

Disclosures None.

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