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Effects of Vitamin D and Marine-Derived Omega-3 Fatty Acid Supplementations on Inflammation and Clinical Outcomes in Autoimmune Diseases: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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ABSTRACT

Objective: Vitamin D and omega-3 fatty acids are proposed immunomodulatory therapies due to their anti-inflammatory properties in autoimmune diseases. However, evidence remains inconsistent. This meta-analysis evaluates their impact on inflammation and disease activity in autoimmune diseases.

Methods: A systematic search (June 24–July 21, 2024) was conducted using PubMed, ScienceDirect, Google Scholar, and Cochrane Library. Eligible randomized controlled trials assessed vitamin D or marine-derived omega-3 fatty acids on inflammatory biomarkers (CRP as primary outcome) in autoimmune diseases, including rheumatoid arthritis, systemic lupus erythematosus, and psoriasis. Study quality was assessed using the Cochrane Risk-of-Bias tool, with heterogeneity evaluated via I^2 in a random-effects model using RevMan.

Results: Nineteen RCTs (1,827 participants) were included; 15 qualified for meta-analysis. Neither vitamin D nor omega-3 supplementation significantly reduced CRP levels. Vitamin D improved VAS-pain scores in RA (SMD: –0.22; 95% CI: –0.45 to –0.00; I^2 = 0%; p = 0.05). Omega-3 significantly reduced Tender Joint Count (SMD: –1.59; 95% CI: –2.73 to –0.46; I^2 = 70%; p = 0.006) and showed a statistically significant effect on IL-6 levels (SMD: 0.56; 95% CI: 0.02 to 1.10; I^2 = 65%; p = 0.04) in RA; however, this finding was inconsistent across individual studies and should be interpreted cautiously. No significant effects were observed for SLE or psoriasis. Funnel plots were not considered reliable for assessing publication bias due to the limited number of studies. Risk-of-bias assessment rated 2 studies as low risk, 7 as moderate, and 10 as high risk.

Conclusion: Vitamin D and omega-3 fatty acid supplementation showed no significant effect on CRP levels and limited, inconsistent effects on clinical outcomes in autoimmune diseases. The overall evidence remains inconclusive due to small sample sizes, heterogeneity, and risk of bias. Larger, well-designed randomized controlled trials are required to confirm these findings.

Keywords: Vitamin D; Marine Omega-3 Fatty Acid; Rheumatoid Arthritis; Systemic Lupus Erythematosus; Psoriasis.

INTRODUCTION

Immune system dysregulation is a characteristic of autoimmune disorders, including psoriasis, systemic lupus erythematosus (SLE), and rheumatoid arthritis (RA), which afflict 5–10% of the world's population [1,2]. RA is a chronic autoimmune disease with a global burden of 0.24% of the world's population [3] that typically impacts the joints, causing pain and inflammation that can progress to joint damage if left untreated. It is characterized by an immune attack on the synovium (joint lining), resulting in joint swelling and decreased function, and may also give rise to systemic issues affecting other organs and tissues. Another autoimmune disorder, SLE, is a chronic illness in which healthy tissues are attacked by the body's immune system, triggering inflammation and damage to various organs including skin, joints, kidneys, and the brain, with a global incidence of 5.14 cases per 100,000 person-years [4]. Multiple symptoms, including joint discomfort, rashes, and fatigue, can be associated with this illness. Psoriasis is another chronic autoimmune disorder affecting the skin, characterized by rapid turnover of skin cells, resulting in thick, red, scaly patches often observed as plaques. The prevalence of psoriasis is estimated at 2–4% worldwide, although reported rates vary significantly between regions and populations [5].

The immunopathogenesis of RA, SLE, and psoriasis is complicated by genetic predisposition and environmental variables. In RA, pro-inflammatory cytokines such as TNF-α and IL-6 are produced as a result of environmental stimulus on innate immunity, leading to synovial swelling and joint damage [6]. SLE is differentiated by loss of self-tolerance, in which autoantibodies target different body tissues due to dysregulated T- and B-cell responses and heightened stimulation of innate immunity [7]. Psoriasis is marked by hyperactivation of the innate immune system, specifically through the IL-23 and IL-17 pathways, contributing to keratinocyte proliferation and skin-surface inflammation [8]. Despite advances in conventional therapy, many patients still endure poor disease control, side effects, and reduced quality of life, highlighting the need for adjunctive therapy [9].

Vitamin D receptors are expressed on immune cells, exerting a direct effect on immune-cell activity and cytokine production [10]. Studies indicate that, through modulating immunological responses, vitamin D supplementation reduces disease activity and enhances quality of life in individuals with RA and SLE [11,12]. Moreover, vitamin D deficiency has been associated with an elevated risk of autoimmune disease, indicating a potential preventive role [13].

The anti-inflammatory properties of marine-derived omega-3 fatty acids, especially eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are attributed to inhibition of NF-κB signaling, regulation of immune-cell function, and reduction of oxidative stress [14]. Supplementation with omega-3 fatty acids has demonstrated efficacy in reducing inflammation while improving symptoms in patients with RA [15].

However, inconsistent findings, small sample sizes, and varying supplementation protocols limit the current evidence base for vitamin D and omega-3 fatty acid supplementation in RA, SLE, and psoriasis. To address these knowledge gaps, this systematic review addresses the following research questions: (1) What are the effects of vitamin D supplementation on inflammatory biomarkers and clinical outcomes in patients with RA, SLE, and psoriasis? (2) What are the effects of omega-3 fatty acid supplementation on inflammatory biomarkers and clinical outcomes in patients with RA, SLE, and psoriasis?

Clarifying the role of vitamin D and omega-3 fatty acids in immunomodulation will guide future research, enhance therapeutic outcomes, and potentially benefit the millions of people affected by autoimmune diseases such as

psoriasis, RA, and SLE. This review synthesizes the available evidence, highlighting the benefits and limitations of these adjunctive strategies for reducing disease severity and improving quality of life.

METHODS

Protocol Information

The PRISMA-P guidelines were followed in developing the protocol for this systematic review, which was registered in PROSPERO (Registration No.: CRD42024561879). The main objective of the review is to evaluate the effects of marine omega-3 fatty acids and vitamin D supplementation in autoimmune diseases. The protocol specified the eligibility criteria, search strategy, and data extraction methods in advance. The study was exempt from ethical review approval.

Search Strategy

Two independent reviewers performed a comprehensive literature search to identify randomized controlled trials (RCTs) investigating the effect of omega-3 fatty acid and vitamin D supplementation on clinical outcomes and inflammatory biomarkers among patients with autoimmune disorders. Searches were initially conducted for five conditions – rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), psoriasis, type 1 diabetes mellitus (T1DM), and multiple sclerosis (MS) – but T1DM and MS were excluded due to an insufficient number of eligible studies.

Relevant databases, including PubMed, Cochrane Library, Embase, and Google Scholar, along with a manual search, were used to identify eligible studies. The following terms were used as predefined Medical Subject Headings (MeSH): “rheumatoid arthritis, systemic lupus erythematosus, psoriasis, vitamin D, omega-3 fatty acids.” The final search update was performed on 21 July 2024, and studies published between 2001 and 2024 were included (see Supplementary File S1).

Eligibility Criteria

RCTs including adult participants (≥18 years) diagnosed with an autoimmune disorder – notably psoriasis, SLE, or RA – were considered. Eligible studies examined the effects of omega-3 fatty acids (EPA, DHA, n-3 PUFA) or vitamin D (ergocalciferol, cholecalciferol, calcitriol) against placebo as the sole comparator. Studies were screened against the primary outcome of this review, CRP. Non-English articles, observational studies, and case reports were excluded.

PICOS

Population: Men ≥50 years and women ≥55 years were the initial inclusion criteria; due to a lack of studies within this age band, the criterion was broadened to adults ≥18 years (men and women) with autoimmune disease (psoriasis, SLE, or RA) diagnosed by any recognized criteria.

Intervention: Vitamin D or marine omega-3 fatty acid supplementation.

Comparison: Control group (placebo – no vitamin D or n-3 fatty acids).

Outcome: Primary outcome – C-reactive protein (CRP) levels. Secondary outcomes – quality-of-life scores, patient-reported outcomes, and inflammatory biomarkers beyond CRP.

Study Design: Randomized controlled trials.

Data Gathering and Choice of Study

Study selection was conducted independently by two reviewers using Rayyan.ai. Discrepancies were resolved through discussion, with a third reviewer adjudicating unresolved conflicts; no automated or randomized selection process influenced inclusion. Four reviewers performed data extraction to ensure comprehensive capture of the required information, and two reviewers performed duplicate detection. Studies that did not meet the predefined inclusion criteria were excluded from the final analysis.

Management and Extraction of Data

A standardized data-extraction form was used by four independent reviewers to extract data from eligible studies. Study characteristics (author, publication year, country, duration, study design, etc.) and participant details (sample size, age, gender, autoimmune-disease diagnosis, and baseline characteristics) were recorded. Intervention specifics – vitamin D or omega-3 fatty acid type, dosage, duration, and route of administration – along with data from the placebo control group were also extracted (see Table 1). The primary outcome was CRP level; additional inflammatory biomarkers and clinical outcomes were analyzed as secondary outcomes where reported. Disagreements between reviewers were resolved by a senior team member.

Assessment of Risk of Bias

The Cochrane Risk of Bias 2.0 tool was used to evaluate risk of bias in each included study across five domains: the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. Each domain was rated as low, some concerns, or high risk according to established standards. Assessment was performed independently by two reviewers, with disagreements resolved through discussion. A risk-of-bias table was compiled to summarize methodological quality and inform the overall certainty of findings (see Table 2).

Table 2. Quality Assessment (Cochrane Risk of Bias 2.0)

STUDY	D1	D2	D3	D4	D5	OVERALL
Sundrarjun et al 2004	Some concerns	Low	Some concerns	Some concerns	Some concerns	Some concerns
Soubrier et al 2018	Some concerns	Low	Low	Low	Some concerns	Some concerns
Fatel et al 2021	Some concerns	Some concerns	Low	Low	Low	Some concerns
Disphanurat et al 2019	Some concerns	Low	Some concerns	Low	Low	Some concerns
Karimzadeh et al 2017	Some concerns	Low	High	High	Some concerns	High
Arriens et al 2015	High	Some concerns	High	Some concerns	Some concerns	High
Kristensen et al 2017	Low	Low	Low	Low	Some concerns	Some concerns
Buondonno et al 2017	Some concerns	Some concerns	High	Low	Some concerns	High
Li et al 2016	Low	Low	Low	Low	Low	Low
Ingram et al 2018	Some concerns	Low	Low	Low	High	High
Rajaei et al 2015	Some concerns	High	High	Low	Some concerns	High
Berbet et al 2004	Some concerns	High	High	High	Some concerns	High

STUDY	D1	D2	D3	D4	D5	OVERALL
Nielsen et al 2021	Low	Low	Low	Low	Some concerns	Some concerns
Bahadori et al 2010	Some concerns	High	High	High	High	High
Kristensen et al 2016	Some concerns	Some concerns	High	Low	Some concerns	High
Park et al 2012	Some concerns	High	Low	Low	Some concerns	High
Wright et al 2007	Some concerns	High	Low	High	Low	High
Partan et al 2022	Some concerns	High	Low	Low	Some concerns	High
Kolahi et al 2009	Some concerns	Some concerns	Low	Low	Some concerns	Some concerns

D1: bias arising from the randomization process. D2: bias due to deviations from intended interventions. D3: bias due to missing outcome data. D4: bias in measurement of the outcome. D5: bias in selection of the reported result.

Data Synthesis

Review Manager (RevMan 5.4) was used for data synthesis, with analysis performed by two research members. The change in CRP level in response to supplementation with vitamin D or omega-3 fatty acid was the primary outcome of interest, with the standardized mean difference (SMD) used as the effect measure. Where studies reported medians, interquartile ranges (IQR), standard errors of the mean (SEM), 95% confidence intervals (CI), or minimum–maximum values, data were converted to approximate means and standard deviations using established conversion formulas (see Supplementary File S2).

Forest plots were generated using the continuous data retrieved for the intervention and control groups, including means and standard deviations. The Chi² test and I^2 statistic were used to assess heterogeneity among studies; a significance level of $p < 0.05$ or $I^2 > 50\%$ indicated substantial heterogeneity. A random-effects model was applied throughout to account for variation in demographics and interventions. Funnel plots were used to evaluate potential publication bias, with asymmetry interpreted as a possible indicator of bias or small-study effects. Sensitivity analyses were not performed owing to the limited number of studies available for each outcome, which restricted meaningful subgroup or robustness analysis.

RESULTS

Study Selection

A comprehensive search of the Cochrane Library, PubMed, Embase, and Google Scholar databases retrieved a total of 3,413 articles. After removing duplicates and completing full-text screening, 9 articles met the predetermined inclusion criteria; a subsequent manual search identified a further 10 studies. In total, 19 studies were included in the qualitative synthesis and 15 in the quantitative synthesis (meta-analysis) (Figure 1).

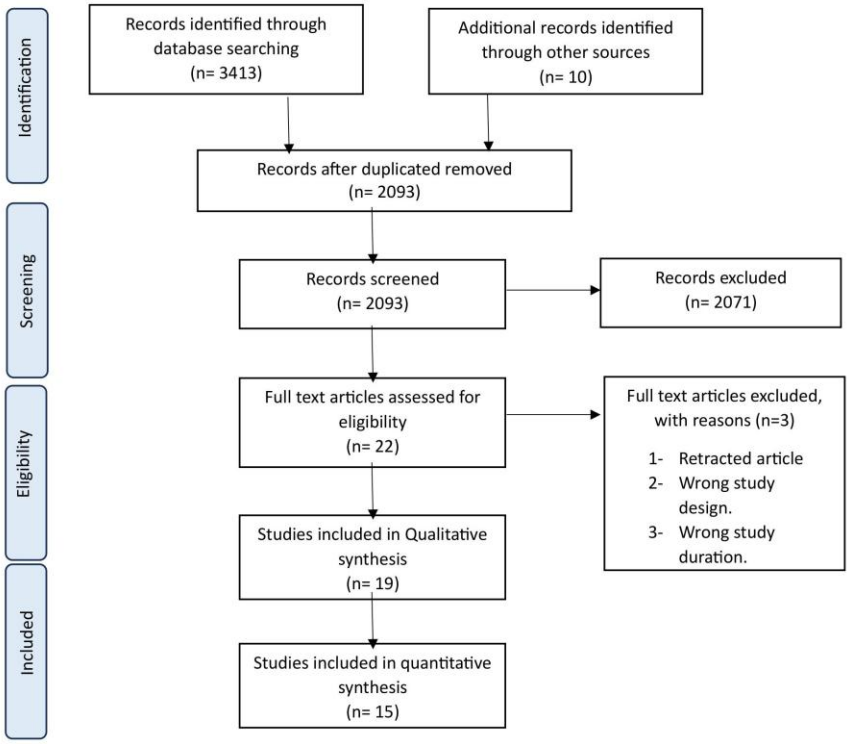

Figure 1. Flow chart of study selection process

This figure illustrates the literature search and selection process for randomized controlled trials assessing the effects of vitamin D and omega-3 fatty acids on inflammation in autoimmune diseases.

Study Characteristics

The characteristics of the included studies are summarized in Table 1. A total of 1,827 participants from 19 studies were evaluated. Randomized controlled trials addressing psoriasis, SLE, and RA were included. Interventions varied, with 7 studies investigating vitamin D supplementation and 12 studies investigating omega-3 fatty acids. Doses of vitamin D and omega-3 fatty acids ranged from 665 to 300,000 IU and 1 to 4.5 g, respectively, and treatment duration ranged from 6 to 48 weeks. Most studies were conducted in Denmark, Iran, Brazil, and Thailand, with additional contributions from France, Texas (USA), China, New Zealand, Indonesia, Austria, Korea, and the United Kingdom. Follow-up periods ranged from 6 to 36 weeks.

Table 1. Characterization of the included studies

Reference	Country	Autoimmune Disease	Type of Blinding	Sample Size	Age and Gender	Participants/ Definition	Intervention	Study Duration	Outcome	Results and Key findings	Statistical Measure	Conclusion	Quality Assess-ment
Sundrarjun et al (2004) [16]	Thailand	RA	Double Blinding	60	46.2 ± 0.5 yrs (F= 51 M =9)	Active RA patients defined as the presence of at least 3 of the following criteria: 6 or more tender joints, 3 or more swollen joints, >30 minutes of morning stiffness, ≥ 28 mm/h ESR rate [All receiving DMARDs for 3 months at least prior to studies].	Intervention group (n = 23) 4 capsules (3.36 g/day) of Fish Oil (n-3 PUFA) + low n-6 PUFA diet. Each capsule equivalent to 470 mg EPA and 310 mg DHA. Control group 1 (n=23) n-3 PUFA placebo + low n-6 PUFA diet. Control group 2 (n=14) no change in diet.	24 weeks	Outcomes include tender and swollen joint count performed by a rheumatologist (SA) and VAS pain score, PGA and MHAQ. Total serum FAs were analyzed using gas chromatography, 19 Serum CRP concentrations by automatic Behring Nephelometer 100, 20 Serum IL-6, TNF-α and sTNF-R p55 were analyzed using an ELISA kit and ESR by Westergren method.	1. Serum IL-6: Fish oil [basal = 93.57 ± 15.56, 24 weeks = 58.77 ± 8.99] Placebo [basal = 60.95 ± 12.57, 24 weeks = 39.58 ± 8.43] 2. CRP (mg/l): Fish oil [basal = 51.12 ± 9.13, 24 weeks = 34.65 ± 8.27] Placebo [basal = 29.15 ± 5.63, 24 weeks = 21.34 ± 5.98]. 3. VAS: Fish Oil [basal= 45.86 ± 4.07, 24 weeks= 47.14 ± 4.36] Placebo [basal= 55.86 ± 5.48, 24 weeks= 33.44 ± 4.30.	mean ± SEM	At week 24 there were significant reductions in interleukin-6 and TNF-α in the fish oil and placebo groups. Supplementation with n-3 FA and a low n-6 FA intake decreased serum sTNF-R p55 and CRP levels in patients with RA.	Some concerns
Soubrier et al (2018) [17]	France	RA	Double Blinding	59	59.8 ± 10.9 yrs (83.1% F)	RA patients greater than 18 years according to the revised 1987 ACR criteria, with RA for 17.0±9.7 years, being in non-remission (DAS 28>2.6), display serum 25[OH]D levels <30 ng/ml, with no treatment modification within the last 3 months.	Intervention group (n=29) Vitamin D (100,000 IU Cholecalciferol vial). Control group (n=30) Vitamin D placebo.	36 weeks	Disease activity based on HAQ, DAS28-ESR, DAS28-CRP, swollen and tender joint count, VAS for pain and activity, ESR, and CRP, EULAR response, decrease in asthenia (VAS and FACIT-fatigue), and improvement in RAID score. The impact of vitamin D supple-mentation on quality of life was assessed using the 36-Item Short Form Health Survey (SF-36).	1. HAQ score: Vitamin D [basal = 1.05±0.74, 6 months = -0.03 ± 0.23] Placebo [basal = 1.05±0.74, 6 months = ± 0.08 ± 0.25] 2. ESR: Vitamin D [p = 0.002] 3. CRP: Vitamin D [p = 0.04].	mean ± (SD) or median with (IQR)	At 6 months, HAQ scores tended to be slightly decreased in the vitamin D group (p=0.11). No significant difference in secondary criteria observed between the 2 groups except for ESR and CRP (p=0.002 and 0.04, respectively).	Some concerns
Fatel et al (2021) [18]	Brazil	RA	Single Blinding	62	43-65 yrs (F=50, M=12)	RA patients recruited from the Rheumatology Outpatient Center of the University Hospital of Londrina; Brazil based on the parameters from the 2010 American College of Rheumatology/EuropeanLeague Against Rheumatism classification criteria.	Intervention Group (n=21) 3 gm of fish oil/day [3 times=10 capsules]. Each capsule contains 180 mg of EPA and 120 mg of DHA originating from Sardines. Control group 1 (n=21) typical diet. Control group 2 (n=22) 3 gm of fish oil (n-3 FAs) [10 capsules] and	12 weeks + 6 days	Disease activity status was assessed using the CRP modification of the DAS28. Serum hsCRP and Rheumatoid Factor (RF) were analyzed by immunoturbidimetric assay, AntiCCP levels by a chemiluminescence microparticle immunoassay, IL-6 levels by ELISA, Plasma	1. CRP (mg/dL): Fish oil [basal = 5.5 (2.0-9.5), 90 days = 3.9 (1.7-11.1)] Control [basal= 3.7 (1.9-5.5), 90 days= 7.1 (3.9 - 12.6)] Cranberry [basal= 3.7 (1.7-7.5), 90 days= 2.5 (1.9-5.1)]. 2. IL-6, pg/mL: Fish oil [basal = 5.46 (2.59-15.21), 90 days = 10.18 (4.29-20.62), Control [basal= 6.34 (2.74-18.91), 90	median (IQR)	The fish oil group showed decreased DAS28-CRP and adiponectin. The study confirms beneficial effects of fish oil supplements on disease activity in RA. Furthermore, cranberry juice would add beneficial effects to fish oil by decreasing disease activity and inflammatory biomarkers.	Some concerns

Reference	Country	Autoimmune Disease	Type of Blinding	Sample Size	Age and Gender	Participants/ Definition	Intervention	Study Duration	Outcome	Results and Key findings	Statistical Measure	Conclusion	Quality Assess-ment
							500 ml/day of reduced caloric cranberry juice at Breakfast and Dinner.		concentrations of adiponectin and leptinby a sandwich ELISA, and ESR by theautomated kinetic-photometric method.	days= 3.25 (1.27-12.99), Cranberry [basal= 3.24 (1.00-5.51), 90 days= 1.00 (1.00-2.14).			
Disphanur-at et al (2019) [19]	Thailand	Psoriasis	Double Blinding	45	18-70 (FM=24, M=21)	Patients with chronic Plaque type Psoriasis, aged 18-70 years and those with mild Psoriasis [PASI score<10]	Intervention group (n=23), F=13 and m=10. Vitamin D2 (60,000 IU Cholecalciferol) 3 capsules every 2 weeks for 6 months. Control group (n=22) 3 capsules of placebo every two weeks for 6 months	24 weeks	The primary outcome was improvement of the PASI score after 3 and 6 months. The secondary outcomes were serum 25(OH)D concentration. Vitamin D deficiency was defined as a serum 25(OH) vitamin D level <20 ng/ml, and vitamin D insufficiency as a serum 25(OH) vitamin D level of 21–29 ng/ml. Laboratory parameters, include serum calcium, phosphate, parathyroid hormone, and Crp.	1. PASI score: Vitamin D2 [Basal = 4.68±3.12, 6 month= 2.39±1.97] Control [basal= 4.21±2.53, 6 months= 3.35±2.49]. 2. Serum 25(OH)D level (ng/mL): Vitamin D2 [basal= 24.77±5.42, 6 month= 27.39±5.89] Control [basal= 24.13±7.74, 6 month= 22.44±7.28]. 3.CRP level (mg/L): Vitamin D2 [basal= 6.94±6.65, 6 month= 5.67±7.35] Control [basal= 3.7±4.44, 6 month= 3.99±0.32].	mean ± standard deviation (SD)	At the 6-month follow-up, the mean PASI score in the vitamin D group continuously decreased which represented improvement from base-line. The higher 25(OH)D level was associated with lower severity of psoriasis. Study demonstrated improvement of mild psoriasis with oral vitamin D2 supplementation.	Some concerns
Karimzadeh et al (2017) [20]	Iran	SLE	Double Blinding	90	Intervention = 33.78 ± 6.2, Control = 35.69 ± 6.8 (FM=81, M=9)	Patients > 18 years referred to rheumatologic clinic of AlZahra Hospital, affiliate to Isfahan University of Medical Sciences (Isfahan, Iran) who fulfill 4 of the American College of Rheumatology (1982) classification criteria for SLE, and had serum Vitamin D level <30 ng/ml	Intervention group (n=45) F=40, M=5.Vitamin D3 (50,000 IU)/week for 12 weeks and then 50,000 units/month for 6 months. Control group (n=45) F=41, M=4. Vitamin D placebo.	36 weeks	Disease activity was measured using SLEDAI. Serum concentration of 25(OH)D was analyzed using the chemiluminescent immunoassay (CLIA) method. ESR and CRP were measured by standard kits and using an autoanalyzer, C3 and C4 by nephelometry, anti-double stranded DNA (dsDNA) by ELISA Kit. Urine samples were obtained for proteinuria and hematuria.	1. SLEDAI 2K score: Intervention [basal= 3.09±2.36, 36 weeks = 1.62 ± 1.25] Control [basal= 3.09±1.25, 36 weeks= 1.98 ± 2.47]. 2. 25(OH)D (ng/ml): Intervention [basal= 17.36±4.26, 36 week= 37.69 ± 5.92] Control [basal= 16.78±4.39, 36 weeks= 16.62 ± 4.61]. 3. Hs CRP: Intervention [basal= 7 (15.6), 36 weeks= NI] Control [basal= 7 (15.6), 36 weeks= NI].	mean	The findings indicated that though the serum level of Vitamin D increased significantly after Vitamin D supplement administration, the level of SLEDAI did not improve significantly. It is suggested that using Vitamin D in patients with SLE could not have better outcomes in this regard.	High
Arriens et al (2015) [21]	Texas	SLE	Single Blinding	50	18-64 (F=42, M=8)	SLE patients according to 1997 revised American College of Rheumatology criteria carried out in outpatient rheumatology and nephrology clinics in a large urban hospital inDallas, Texas.	Intervention (n=25, completers=18) Fish oil (6 capsules/day = 2.25 gm of EPA and 2.25 gm of DHA Metagenics) + background therapies. Control	24 weeks	Disease activity assessed using SELENA-SLEDAI score and VAS. The renal parameters of the SELENA SLEDAI in the 24 completer patients with lupus nephritis. Quality of life with	1. SELENA-SLEDAI: Fish oil (−1.00[−4.5–4.25]), Control (0.00 [−0.50–2.00]). 2. FSS: Fish oil (−0.056 [−1.500 – 0.500]), Control (0.222 [−0.556–0.667).	median and (IQR)	PGA indicates improvement with Fish Oil therapy. The measure of systemic inflammation ESR shows significant reduction in Fish Oil group. Among cytokines/chemokines/growth factors studied, increase in IL-13 and decrease in IL-12	High

Reference	Country	Autoimmune Disease	Type of Blinding	Sample Size	Age and Gender	Participants/ Definition	Intervention	Study Duration	Outcome	Results and Key findings	Statistical Measure	Conclusion	Quality Assess-ment
							(n=25, completers=14) visually identical placebo (6 capsules/ day) [Purified/refined not extra-virgin Olive Oil Metagenics] + background therapies.		RAND SF-36. Fatigue was assessed with the Fatigue Severity Scale (FSS). Serum soluble mediator panel assessed using the Luminex magnetic 30-plex human cytokine panel. C3, C4, ds DNA antibody, ESR, CRP, lipid panel, and spot urine protein to creatinine ratio were assessed.	3.PGA: Fish oil (−0.550 [−1.275– -0.100]), Control (0.50 [−0.200– 0.350]). 4. ESR: Fish oil (−5.0 [−39.0– -2.5]), Control (4 .5 [0.0– 19.0]).		demonstrates improvement in Fish oil group.	
Kristensen et al (2017) [22]	Denmark	Psoriatic Arthritis	Double Blinding	145	52.0 ± 11.5 (F=83, M=60)	Psoriatic arthritis patients, defined by classification criteria for Psoriatic Arthritis and age >18 years. Over a 2-year period, consecutive patients with established PsA attending the Department of Rheumatology, Aalborg University Hospital, and the Department of Rheumatology, North Denmark Regional Hospital, Denmark.	Intervention group (n=72): 6 capsules containing 3 g of n-3 PUFA (50% EPA and 60%DHA) Control group (n=71): 6 capsules of placebo contain 3 gm of Olive oil (approximately 80% Oleic Acid and 20% Linoleic Acid [LA]). Healthy Controls (n=57).	24 weeks	The clinical assessment include: 68 tender joint count, 66 swollen joint count, Disease Activity Score based on CRP (DAS28-CRP), VAS (pain), HAQ, and PASI. Blood samples were obtained in a non-fasting state for routine laboratory evaluation including plasma levels of CRP.	1. VAS-pain: n-3 PUFA [basal= 29.73, 24 weeks= 30.12] Control [basal= 36.69, 24 weeks= 34.45] 2. HAQ: n-3 PUFA [basal= 0.69, 24 weeks= 0.70] Control [basal= 0.76, 24 weeks= 0.78]. 3. TJC (68): n-3 PUFA [basal= 5.10, 24 weeks= 2.67] Control [basal= 4.16, 24 weeks= 4.10]. 4. SJC (66): n-3 PUFA [basal= 0.61, 24 weeks= 0.30] Control [basal= 0.87, 24 weeks= 0.84]. 5. CRP (mg/L): n-3 PUFA [basal= 4.6±4.2, 24 week= 4.98±4.47] Control [basal= 6.1±7.7, 24 week= 6.93±9.52].	means with 95% confidence intervals	The n-3 PUFA group showed non-significant improvement in outcome measures for disease activity. However, use of NSAIDs was significantly reduced in the n-3 PUFA group compared to the control group. Finally, there was a significant decrease in leukotriene B4 formation in the n-3 PUFA group compared with controls.	Some concerns
Buondon-no et al (2017) [23]	Italy	RA	Double Blinding	70	eRA patients (n=39) = 54 ± 13 (all F)	eRA patients enrolled in the Rheumatology Unit, Ospedale Mauriziano, andin the Rheumatology Department, AOU Città della Salute e della Scienza di Torino, Torino, Italy. F ≥18 years of age with a diagnosis of RA, as defined by the American College of Rheumatology 2010 criteria for <6 months prior to inclusion in the study.	RA patients (n= 21) = Methotrexate 15 mg/week (IM or SC) and methyl-prednisolone per oz. 2–4 mg/day +Cholecalciferol 300,000 IU. Placebo group (n=18) = Methotrexate 15 mg/week (IM or SC) and methyl-prednisolone per oz. 2–4 mg/day + Placebo.	12 weeks	The outcome measures of the study were changes in numberof Tregs (measured by flow cytometry), CD4+ cells and OCs precursors (by flow cytometry, Inflammatory Cytokines including IL 17, IL 23, IL 6, TGFβ1, TNF-α, and RANKL (by ELISA) and clinical parameters including DAS 28, CRP, ESR,	1. HAQ: Cholecalciferol [basal= 1.4±0.7, Control= 1.3±1.0]. 2. VAS pain: Cholecalciferol [basal= 68.3±18.9, Control= 57.5±20.6]. 3. ESR: Cholecalciferol [basal= 38 (23.5–59), Control= 38 (17.5–60.0)]. 4. CRP (mg/L): Cholecalciferol [basal= 12.35 (5.5–	Mean ± SD for Gaussian variables, for non-Gaussian variable: median (25–75 percentiles)	After 3 months, an increased level of non-classical OCs precursors and pro-inflammatory cytokines was observed. Vitamin D combined with standard treatment significantly ameliorates patients' general health.	High

Reference	Country	Autoimmune Disease	Type of Blinding	Sample Size	Age and Gender	Participants/ Definition	Intervention	Study Duration	Outcome	Results and Key findings	Statistical Measure	Conclusion	Quality Assess-ment
									HAQ, and VAS Pain Score.	23.5), Control= 10.0 (2.5–31.0)].			
Li et al (2018) [24]	China	RA	Double Blinding	369	Placebo group = 51.12±10.23 Treatment group =48.47±11.12 Control group = 49.58±10.57	RA Patients >18 years, recruited from the Department of Orthopedics of the Affiliated Hospital of Xuzhou Medical University, Xuzhou, China, as per ACR/EULAR criteria defined as at least 4 swollen joints (out of 70 examined).	Placebo group (n=123) = lactose powder 5 g/week, 50 000 IU/week, Treatment group (n=123) = 22-oxa-calcitriol (1 IU of 22-oxa-calcitriol = 25 ng of 22-oxa-calcitriol), Control group (n=123) = 50 000 IU/week calcitriol (1 IU of calcitriol = 25 ng of calcitriol). All supplements were continued for 6 weeks	6 weeks	Functional status or disability evaluated by HAQ-DI. Serum vitamin D levels by radioimmunoassay method, ESR, CRP, serum calcium test by modified Arsenazo method. Secondary Outcomes include swollen joints count, duration of morning stiffness, and visual analog scale (VAS) score for pain.	1. CRP (mg/dL): Treatment [basal=1.91±0.09, 6 weeks= 1.61±0.12] Placebo [basal= 1.81±0.71, 6 weeks=1.79±0.72]. 2.VAS: Treatment [basal= 6.12 ±0.59, 6 weeks=5.15±0.81] Placebo [basal=5.91±0.51, 6 weeks=5.89±0.53]. 3. HAQ-DI: Treatment [basal=1.33±0.77, 6 weeks= 1.15±0.1] Placebo [basal= 1.31±0.75, 6 weeks=1.29±0.71].	Constant data as a number (%) and continuous data as mean±SD	Both 22-oxa-calcitriol and calcitriol successfully decreased swollen joints in patients with RA, and both improved HAQ-DI and serum vitamin D levels. The intensity of improvement of serum vitamin D levels in both groups was the same. however, calcitriol caused hypercalcemia.	Low
Ingram et al (2018) [25]	New Zealand	chronic plaque psoriasis	Double Blinding	101	Intervention group (n= 67) 50.7±13.4, Placebo group (n= 34) 46.7 ±13.7 (M=56, F=45)	Chronic plaque psoriasis patients >18 years who completed an online screening questionnaire.Psoriasis treatments used for longer than 3 months immediately prior to the trial were permitted.	Intervention group (n= 67) = Vitamin D3 (cholecalciferol) was given as a monthly mega-dose (200,000 IU at baseline, followed by 100,000 IU/month, equivalent to 3340 IU/ day) taken as gelatin capsules. Placebo group (n= 34) = identical capsules without Vitamin D3.	48 weeks	Psoriasis was assessed by a trained researcher using the PASI score, then classified as mild (<7), moderate (7–12) or severe (>12). Serum 25(OH)D was measured using an automated immunoassay. Serum calcium measured with the Dimension Vista System using the CA method, and serum hsCRP with the Dimension Vista System Cardio Phase method.	1. PASI score: Vitamin D3 [basal= 5.2(3.3, 6.5), 12 months= 3.7(2.0, 6.4)], Placebo [basal= 4.2(3.1, 7.0), 12 months= 3.4(2.4, 4.9)]. 2. Serum 25(OH)D (nmol/L): Vitamin D3 [basal= 62(26)], Placebo [basal= 55 (19)]. 3. hsCRP (mg/L): Vitamin D3 [basal= 1.21(0.94–1.57)], Placebo [basal= 2.01(1.37–2.93)].	Data are number (%), mean (SD), median [25th, 75th percentile], except hsCRP, which are mean [95% CI]	PASI did not differ between groups at any time. However, 25(OH)D increased in both groups. A direct benefit of vitamin D3 supplementation for psoriasis could not be determined. However, the study suggests a relationship between 25(OH)D and psoriasis severity.	High
Rajaei et al (2015) [26]	Iran	RA	Double Blinding	60	42.4 ± 7 years (F=49, M=11)	Active RA patients recruited from Rheumatology Clinic of Ahvaz Golestan Hospital, defined according to the Association of Rheumatology America (ACR) criteria and selection by two rheumatologists after clinical evaluation and diagnosis of their illness.	Omega 3 group (n=30) = 2 O3FA capsules daily which contained 1.8 gm of EPA and 2.1 gm of DHA + Standard Therapy. Placebo group (n=30) = identical starch capsules+ standard therapy.	12 weeks	Patients were evaluated every four weeks for three months in terms of clinical and laboratory findings, including ESR, CRP, daily analgesic consumption, SJC, TJC, duration of morning stiffness in minutes, PhGA, patients' severity of joint pain and the patients' disease activity using VAS.	1. Morning Stiffness: Omega 3 [basal= 128, 12 weeks = 40], Placebo[basal=116, 12 week=94] 2. TJC: Omega 3 [basal= 21, 12 weeks= Placebo [basal= 24, 12 weeks= 20]. 3. SJC: Omega 3 [basal= 10, 12 weeks= 3] Placebo [basal= 7, 12 weeks = 5]. 4. ESR: Omega 3 [basal= 39, 12 weeks= 16] Placebo	mean (SD) for quantitative variables, and frequency for qualitative variables	At the end of the study significant improvement in clinical measures of disease activity in the Omega-3 group was observed. Daily supplementation with omega-3 results has significant clinical benefit and may reduce the need for concomitant analgesic consumption without weight changes.	High

Reference	Country	Autoimmune Disease	Type of Blinding	Sample Size	Age and Gender	Participants/ Definition	Intervention	Study Duration	Outcome	Results and Key findings	Statistical Measure	Conclusion	Quality Assess-ment
										[basal= 35, 12 weeks = 33]. 5. CRP: Omega 3 [basal= 2+, 12 week= 0-1+] Placebo [basal= 2+, 12 week = 2+-3+].			
Berbert et al (2005) [27]	Brazil	RA	no blinding	42	mean age 49 ±19y, (F=34, M=9)	RA patients defined according to the AmericanCollege of Rheumatology criteria were included after clinical evaluation at the Rheumatology OutpatientService of the University ofLondrina (Paraná, Brazil).	G1: Treatment group (n=13) = 3 g/d (20 capsules) of fish oil that contain 90 mg EPA and 60 mg DHA/ capsule, G2: Placebo group (n=13)= Soy Oil, G3: Treatment+ Oleic Acid group (n=17)= 3 g/d of fish oil and 6.8 g of oleic acid (9.6 mL of olive oil)handled in a proper plastic flask filled and was added to salad.	24 weeks	Clinical assessment includes Duration of Morning Stiffness (in minutes); Joint Pain Intensity measured on a five-point scale; PGA of disease activity (0- to 10-cm VAS); and HAQ. Laboratory evaluation includes CRP and RF (by nephelometry), AAG and AAT (by immunoturbidimetry), ESR (Wester green's method), and hemoglobin.	1. Morning stiffness (min): G1 [basal=44±68, 24 week= 5±8], G2 [basal= 38±42, 24 week=51±50], G3[basal=60±65, 24 week= 11±26]. 3. PGA: G1 [basal= 1.54±0.88, 24 weeks= 1.23± 0.60], G2 [basal= 1.25±0.75, 24 weeks= 1.31± 0.95], G3 [basal= 1.82±0.53, 24 weeks= 0.88±0.70]. 2. CRP (mg/dl): G1 [basal= 17.9± 20.3, 24 weeks= 19.5±22.3], G2 [basal= 15.5±21.1, 24 weeks= 18.1±15.8], G3 [basal= 24.8± 31.6, 24 weeks= 17.4±23.8].	mean ± standard deviation.	There was a significant improvement in G 1 and G3 in relation to G2 with respect to disease activity. Ingestion of Omega 3 fatty acids relieved several clinical parameters in RA. However, there was a more significant improvement when olive oil was used in combo with fish oil.	High
Bahadori et al (2010) [28]	Austria	RA	Double Blinding	24	Intervention group (n=11) 58 ± 4 yrs and Placebo group (n= 12) 59 ± 2 yrs [F=23, M=1]	Active RA patients according to the ARA criteria despite ongoing treatment with MTX as DMARDs. To be eligible, stable dosages of MTX of at least 10 mg/week and stable dosages of glucocorticosteroids up to 10 mg/day prednisolone were required 1 month before enrollment.	Intervention Group = 0.20 g of fish oil emulsion/kg body weight, 100 ml== 6.56 g of ω-3 PUFA, comprising 2.82 g of EPA and 3.09 g DHA, 0.20 g α-linolenic acid and 0.45 g of DPA. Placebo group= an equal amount of 0.9% saline.	22 weeks	At each examination, SJC and TJC were determined by manual palpation by a trained physician. ESR and CRP levels were determined in a routine clinical laboratory along with other parameters.	1.SJC: Omega 3 group [basal= 10 (6 - 14), 22 weeks= 1 (0 - 5)], Placebo [basal= 14 (6 - 37), 22 weeks= 8 (4 - 10)]. 2. TJC: Omega 3 group [basal= 18 (10 - 37), 22 weeks= 2.5 (0 - 12)], Placebo [basal= 17 (8 - 41), 22 weeks= 8 (5 - 11)]. 3. CRP, g/L: Omega 3 group [basal= 2.2 ± 1.2], Placebo group [basal= 4.4 ± 4.3].	median (range) or mean ± standard deviation.	Both SJC and TJC were significantly lower in the ω-3 FA group compared with the placebo group during and at the end of oral treatment. CRP levels and ESR were not significantly different between the groups. None of the measured laboratory parameters changed during the study. This study indicates that ω-3 FAs improve clinical symptoms of RA.	High
Nielsen et al (2021) [29]	Denmark	Psoriatic Arthritis	Double Blinding	145	52.0 ± 11.5 (F=83, M=60)	PsA patients, defined by classification criteria for Psoriatic Arthritis and age >18 years. Over a 2-year period, consecutive patients with established PsA attending the Dept. of Rheumatology, Aalborg University Hospital, and the Department of	Intervention group (n=71): 6 capsules containing 3 g of n-3 PUFA (50% EPA and 50% DHA). Control group (n=71): 6 capsules of placebo contain 3	24 weeks	ECM remodeling assessed by a panel of biomarkers including validated ELISAs of collagen type I, III and IV was chosen to assess collagen degradation (C1M, C3M, and C4M,	The ECM biomarkers measuring bone formation, OC, and bone degradation, CTX-I, were not statistically different in PsA patients compared to healthy individuals. A trend	Not Specified	Patients with PsA showed an imbalanced ECM turnover compared to healthy individuals. No major differences were found for the biomarkers when the patients were treated with n-3 PUFA for 24 weeks.	Some Concerns

Reference	Country	Autoimmune Disease	Type of Blinding	Sample Size	Age and Gender	Participants/ Definition	Intervention	Study Duration	Outcome	Results and Key findings	Statistical Measure	Conclusion	Quality Assess-ment
						Rheumatology,North Denmark Regional Hospital, Denmark.	gm of Olive oil (approximately 80% Oleic Acid and 20% Linoleic Acid). Healthy Control (n=57).		respectively) and formation (PRO-C1, PRO-C3 and PRO-4, respectively). Clinical parameters include Swollen and Tender Joint Count, DAS-28, PASI, SPARCC, CRP, and VAS pain score.	towards a decreased level of OC in PsA patients was observed (p=0.06).			
Kristensen et al (2016) [30]	Denmark	Psoriatic Arthritis	Double Blinding	145	52.0 ± 11.5 (F=83, M=60)	PsA patients, defined by classification criteria for Psoriatic Arthritis and age >18 years. Over a 2-year period, consecutive patients with established PsA attending the Dept. of Rheumatology, Aalborg University Hospital, and the Department of Rheumatology,North Denmark Regional Hospital, Denmark.	Intervention group (n=71): 6 capsules containing 3 g of n-3 PUFA (50% EPA and 50% DHA). Control group (n=71): 6 capsules of placebo contain 3 gm of Olive oil (approximately 80% Oleic Acid and 20% Linoleic Acid). Healthy Control (n=57).	24 weeks	Clinical evaluation was performed, consisting of 68 TJC, 66 SJC, DAS 66/68 and PASI. Blood samples were taken non-fasting for assessment of fatty acid composition of granulocytes and CRP.	1. Disease Activity Score: n-3 PUFA group [basal= 2.5 (0.9)], Control [basal= 2.7 (0.9)]. 2. CRP mg/l: n-3 PUFA group [basal= 4.6 (4.2)], Control [basal= 6.1 (7.7)]. 3. PASI: n-3 PUFA [basal= 2.2 (3.0)], Control [basal= 2.3 (4.0)].	mean (sd) or n (%) as appropriate	Marine n-3 PUFA increased RR intervals in patients with psoriatic arthritis which may suggest a protective effect of n-3 PUFA against cardiovascular disease in this population.	High
Park et al (2012) [31]	Korea	RheumatoidArthritis	Double Blinding	109	N-3 PUFA group (n= 41) = 49.24±10.46, Placebo (n=40) = 47.63±8.78 [F=75, M=6]	RA patients based on the ACR criteria recruited from Hanyang University Hospital in Seoul, Eulji University Hospital in Daejun, the Catholic University Hospital in Daegu and the Maryknoll Medical Center in Busan between December 2010 and December 2011. Patients receiving NSAIDs, glucocorticoids or DMARDs were eligible if the dosage had been stable for at least 3 months prior to inclusion.	Intervention group = 5 capsules a day of either n-3PUFA containing2.09 g EPA and 1.165 g DHA Control group= placebo containing sunflower oil with oleic acid.	16 weeks	At baseline and at 8 and 16 weeks, duration of morning stiffness, PhyGA, PatGA, KHAQ score and pain scale were assessed. PGE2, LTB4, TNF-α and IL-6 levels in serum were measured using high-sensitivity ELISA. Briefly, lipids were extracted, methylated to form fatty acid methyl esters (FAMEs) and analyzed by gas chromatography on a GC2010 equipped with a 100-m SP-2560 column.	1. IL-6 (U/L): n-3 PUFA group [basal= 455.26 ± 518.46, 16 weeks= 506.46±542.81], Placebo [basal= 320.63±377.49, 16 weeks= 412.31±394.65] 2. hs-CRP (nmol/L): n-3 PUFA [basal= 25.97±32.17, 16 weeks= 31.22±42.90], Placebo [basal= 32.19±51.44, 16 weeks= 43.95±89.33]. 3. KHAQ: n-3 PUFA [basal= 0.54±0.54, 16 weeks= 0.48± 0.58], Placebo [basal= 0.48± 0.45, 16 weeks= 0.41±0.54].	mean±S.D	N-3 PUFA supplements significantly decreased NSAID requirements and leukotriene B4 levels in patients who weighed more than 55 kg. This study suggests that n-3 PUFA supplementation has no significant effect on RA but may decrease NSAIDs requirement in Korean patients with RA who weight more than 55 kg.	High
Wright et al (2007) [32]	United Kingdom	SLE	Double Blinding	126	Intervention group (n=30) = 48.5±9.1 Placebo group (n=30) = 47.6±9.6 [F=56, M=4]	Patients fulfilling the ACR criteria for the diagnosis of SLE were recruited from the lupus research group at Queen's University Belfast (QUB)	Intervention group (n=30) = Omacor [four capsules per day, providing 1.8 g EPA and 1.2 g DHA. Control group (n=30) = 4	24 weeks	The outcomes include endothelial function as measured by FMD, disease activity (SLAM-R and BILAG) and platelet 8-isoprostanes. An electrocardiogram and full screening	1. Erythrocyte sedimentation rate (mm/h): Fish Oil [basal= 33.8 (30.3), 24 weeks= 32 (31)], Placebo [basal= 19.3 (14.0), 24 weeks= 20 (19)].	mean (SD)	In the fish oil group, there was a significant improvement in SLAM-R, BILAG, FMD and in platelet 8 isoprostanes. Low-dose dietary supplementation with omega 3 in SLE not only has a therapeutic effect on disease activity but also	High

Reference	Country	Autoimmune Disease	Type of Blinding	Sample Size	Age and Gender	Participants/ Definition	Intervention	Study Duration	Outcome	Results and Key findings	Statistical Measure	Conclusion	Quality Assess-ment
							capsules per day of olive oil placebo.		blood tests were performed, including plasma homocysteine concentration, fasting lipid profile, serum antinuclear antibody levels, anti-dsDNA antibodies, anticardiolipin antibodies and complement C3 and C4 levels.	2. C-reactive protein (mg/l): Fish Oil [basal= 9.2 (13.8), 24 weeks= 6 (6)], Placebo [basal= 5.3 (9.5), 24 weeks= 5 (8)]. 3. SLAM-R: Fish Oil [basal= 10.2 (3.1), Placebo= 9.6 (4.2)].		improves endothelial function and reduces oxidative stress and may therefore confer cardiovascular benefits.	
Kolahi et al (2009) [33]	Iran	RA	Double Blinding	90	Intervention group (n=45) = 50 (18–74), Placebo group (n=45) = 50 (19–74), All F	Patients were selected consecutively from Rheumatology Clinic of Tabriz University of Medical Sciences (RCTUMS) between April 2008 and November 2008 according to ACR criteria	Intervention group= Fish Oil (1 g/day) containing 120 mg EPA and 120 mg DHA in addition to conventional therapy for RA. Placebo group = Identical placebo without omega 3 substance.	12 weeks	DAS28 was calculated using the numbers of swollen and tender joints, hs CRP and patient general health by the patient using VAS. Serum OPG, TNFα and sRANKL concentrations were determined by ELISA kits; sRANKL by BioVendor kit, OPG and TNFα by Bender MedSystems GmbH. Hs-CRP was determined by immunoturbidimetry assay.	1. Serum TNFα (pg/mL): Fish oil group [basal= 19.5 (0.00–66.4), 3 months= 17.3 (0.00–69.9)], Placebo [basal= 10.4 (0.00–72.6), 3 months= 12.2 (0.00–92.6)]. 2. hs-CRP (mg/dL): Fish oil group [basal= 5.75 (0.30–14.1), 3 months= 3.90 (0.10–14.8)], Placebo [basal= 4.80 (0.10–14.0) 3 months= 6.10 (0.10–16.5)]. 3. DAS28: Fish oil group [basal= 2.42 (1.11–5.25), 3 months= 2.22 (0.99–6.05)], Placebo [basal= 2.98 (0.99–5.70), 3 months= 2.80 (0.99–6.46)].	median (min-max)	Serum levels of osteoprotegerin increased, although sRANKL, TNFα and sRANKL/osteoprotegerin ratio decreased with Fish oil therapy. Omega 3 could decrease the inflammatory response by lowering of serum TNFα levels and sRANKL/osteoprotegerin ratio..	Some concerns
Partan et al (2022) [34]	Indonesia	RA	Double Blinding	35	Intervention group (n=18) =45 (19-57), Placebo group (n=17) =52 (19-57), F= 32, M=3	RA Patients recruited from Rheumatology Clinic of Dr. Mohammad Hoesin General Hospital, Palembang, according to the ACR criteria.	Intervention group (n=17) = one capsule (500 mL) Seluang fish oil every day, containing approximately 665 IU of cholecalciferol, Control group (n=17) = one capsule of placebo every day.	12 weeks	The outcomes were a change in DAS28-ESR and DAS28-CRP scores generated from the calculation of TJC, SJC, VAS, and ESR or CRP using the following formula: *DAS28-ESR = 0.56 x √TJC + 0.28 x √SJC + 0.07 x In (ESR) + 0.014 x (VAS) *DAS28-CRP=0.56 x √TJC +0.28 x √SJC +0.36 x In (CRP + 1) + 0.014 x (VAS) + 0.96. Changes in IL-6, IL-17, and vitamin D	1. IL-6 (pg/mL): Intervention group [basal= 7.59 (1.78-57.25), 12 weeks= 3.44 (1.5-79.9)], Placebo [basal= 11.21 (1.5-100.30), 12 weeks= 3.76 (1.5-53.6)]. 2. CRP (mg/L): Intervention group [basal= 5.00 (1.60-200.00), 12 weeks= 8.90 (0.50-47.50)], Placebo [basal= 5.00 (1.30-74.20), 12 weeks= 2.30 (0.30-59.70)]. . VAS: Intervention group [basal= 6.59±2.32, 12 week=	median (min-max) or mean±sd.	Reduction of DAS28-ESR and DAS28-CRP demonstrated that the Seluang fish oil supplementation was useful in reducing RA disease activity. Seluang fish oil is effective in lowering IL-17 levels, DAS28-ESR, and DAS28-CRP, but not in improving vitamin D level or lowering IL-6 level in RA patients.	High

Reference	Country	Autoimmune Disease	Type of Blinding	Sample Size	Age and Gender	Participants/ Definition	Intervention	Study Duration	Outcome	Results and Key findings	Statistical Measure	Conclusion	Quality Assess-ment
									levels after 12 weeks of supplementation in both groups were also observed.	3.47±2.85], Placebo [basal= 6.76±1.48, 12 week= 4.47±2.00].			

Quality Assessment

The 19 included studies showed varying levels of methodological quality: two were rated low risk of bias, seven moderate, and ten high risk. Figures 2a and 2b present the corresponding risk-of-bias visualizations generated using Cochrane RoB 2.0 standards.

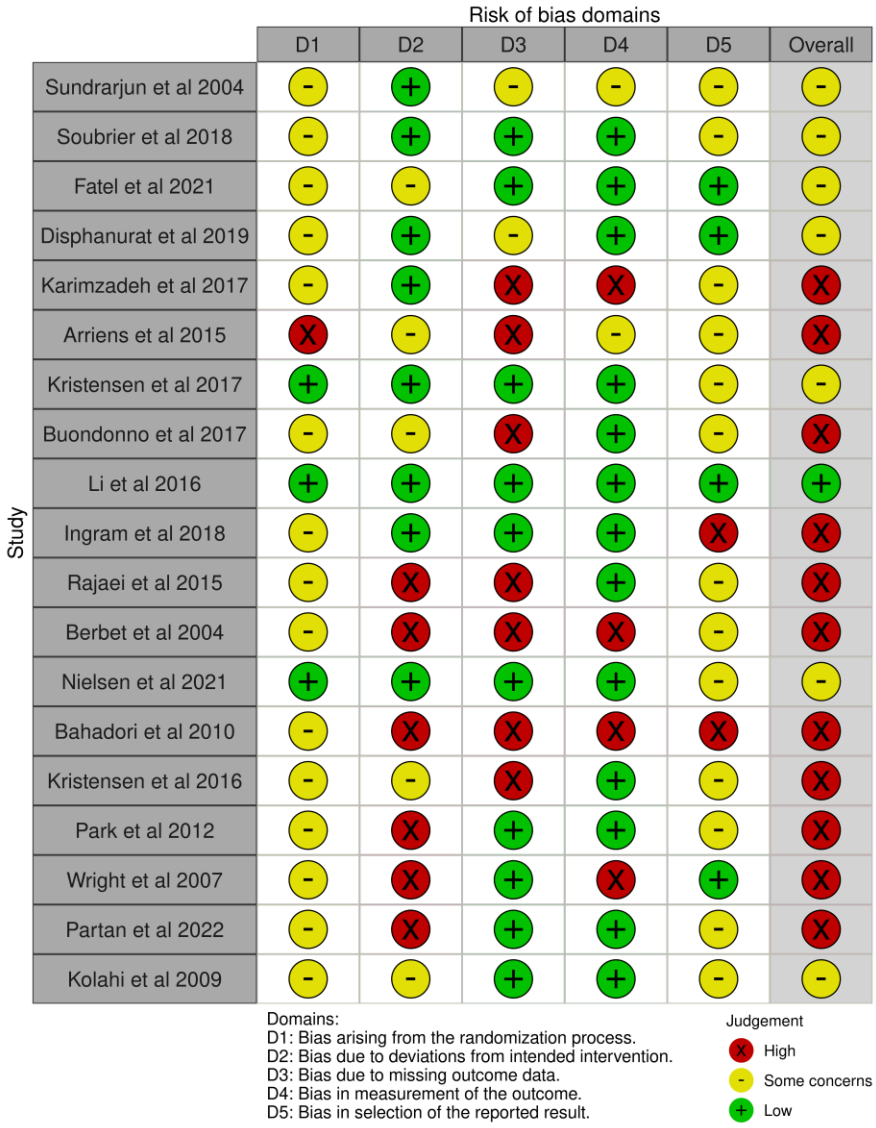

Figure 2a. Risk-of-bias assessment for included studies – traffic-light plot

Traffic-light plot displaying judgments across five RoB 2.0 domains for each included study, with color codes indicating the level of risk of bias.

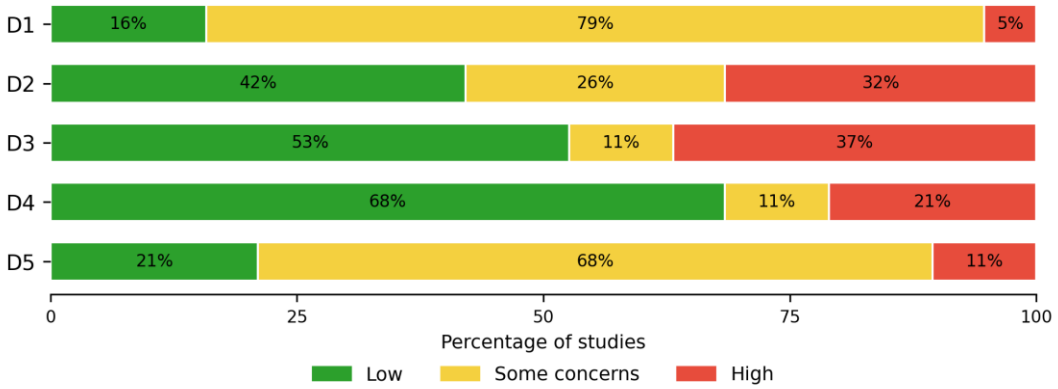

Figure 2b. Risk-of-bias assessment for included studies – summary plot

Summary plot showing the proportion of studies rated as low risk, some concerns, or high risk across each domain of the RoB 2.0 tool.

Findings from Meta-Analysis

This meta-analysis evaluated the effects of vitamin D and marine-derived omega-3 fatty acid supplementation on clinical outcomes in autoimmune diseases by synthesizing data from 15 randomized controlled trials. Standardized mean differences (SMDs) were used in pooled analyses to assess the primary outcome, CRP level, and secondary outcomes including disease-activity scores and quality-of-life measures across RA, SLE, and psoriasis. Where necessary, data were converted to approximate means and standard deviations from medians, IQRs, SEMs, 95% CIs, or minimum–maximum values using established transformation methods (see Supplementary File S2). All forest plots include pooled effect estimates (diamonds) calculated using a random-effects model, with corresponding 95% confidence intervals. The certainty of evidence was evaluated using the GRADE approach, as recommended by the GRADE Working Group [45].

Vitamin D Supplementation: Effects on C-Reactive Protein (CRP)

Four RCTs (n = 316) investigated the effect of vitamin D supplementation on CRP levels in patients with autoimmune disease, specifically RA and psoriasis [19,23,24,34]. The pooled SMD was –0.07 (95% CI: –0.55 to 0.41; p = 0.77), indicating no significant effect of vitamin D compared with placebo on CRP levels. Substantial heterogeneity was observed (I^2 = 71%), possibly reflecting differences in dosage, treatment duration, or participant characteristics.

Subgroup analysis by disease type showed no statistically significant differences (Chi^2 = 1.75; df = 1; p = 0.19; I^2 = 43%). In disease-specific analyses, no significant reduction in CRP was observed for RA (3 studies; SMD: –0.20; 95% CI: –0.70 to 0.29; p = 0.42; I^2 = 63%) or psoriasis (1 study; SMD: 0.31; 95% CI: –0.27 to 0.90; p = 0.30), though the psoriasis result is limited by single-study data. No data were available for SLE (Figure 3).

The certainty of evidence regarding the effect of vitamin D on CRP in RA is low, owing to serious concerns regarding risk of bias, inconsistency, and small sample size (<400) among the studies; the pooled estimate shows no clear benefit or harm and remains inconclusive. Certainty could not be formally assessed using GRADE for the effect of vitamin D on CRP in SLE and psoriasis owing to a lack of studies.

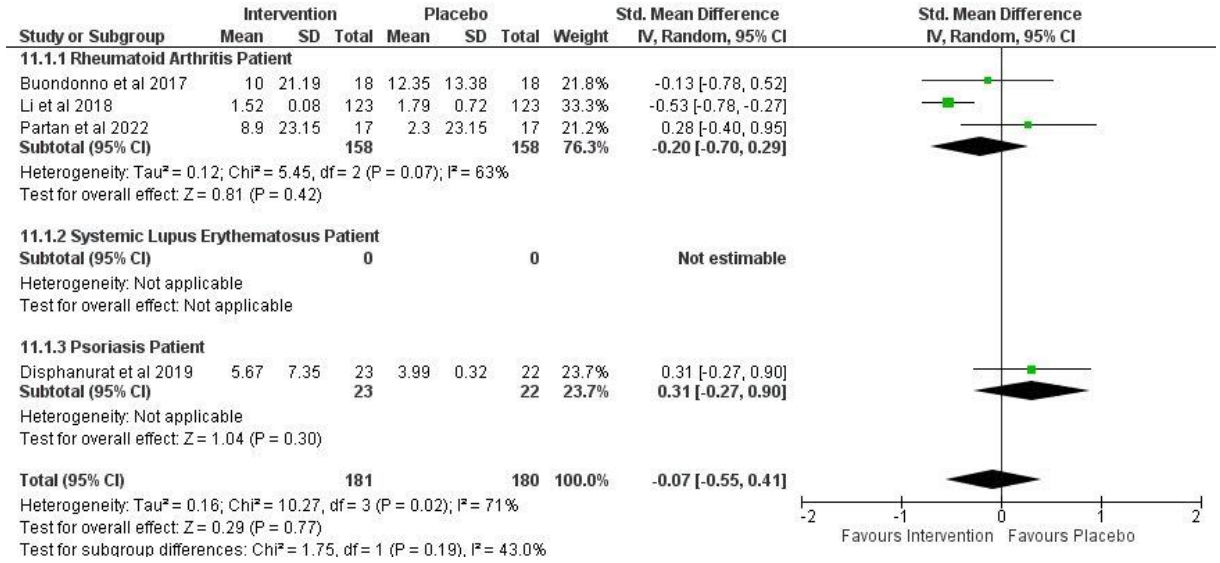

Figure 3. Effect of vitamin D supplementation on CRP levels in autoimmune diseases

Forest plot showing the overall and subgroup effects of vitamin D supplementation compared with placebo on C-reactive protein (CRP) levels in patients with rheumatoid arthritis, systemic lupus erythematosus, and psoriasis. Each square indicates the weight of an individual study, and the diamond represents the pooled effect estimate.

Omega-3 Fatty Acid Supplementation: Effects on C-Reactive Protein (CRP)

Seven RCTs (n = 468) evaluated the impact of marine-derived omega-3 fatty acid supplementation on CRP levels in patients with RA, SLE, and psoriasis [16,18,22,27,31,32,33]. The pooled SMD was 0.00 (95% CI: –0.35 to 0.34; p = 1.00), indicating no statistically significant difference compared with placebo. Substantial heterogeneity was observed (I^2 = 69%).

Subgroup analysis by disease type revealed no statistically significant subgroup differences (Chi^2 = 2.05; df = 2; p = 0.36; I^2 = 2.6%). Disease-specific analyses likewise showed no significant effects: RA (SMD: 0.06; 95% CI: –0.47 to 0.58; p = 0.84; I^2 = 78%), SLE (SMD: 0.14; 95% CI: –0.37 to 0.65; p = 0.59), and psoriasis (SMD: –0.26; 95% CI: –0.61 to 0.08; p = 0.14). Interpretation is limited by substantial heterogeneity within the RA subgroup, small sample sizes, and variability in omega-3 dosage, treatment duration, and baseline CRP levels (Figure 4).

The certainty of evidence regarding the effect of omega-3 fatty acid supplementation on CRP in RA is very low, owing to serious concerns regarding risk of bias, inconsistency, and imprecision among the studies. Certainty could not be formally assessed using GRADE for the effect of omega-3 fatty acids on CRP in SLE and psoriasis owing to a lack of studies.

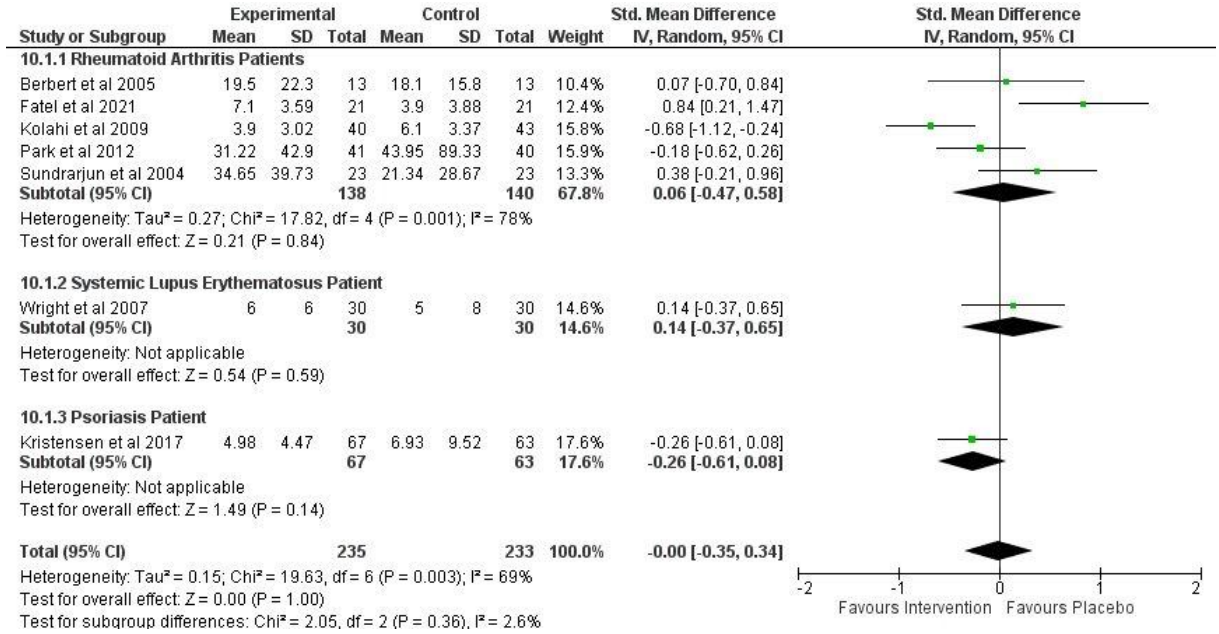

Figure 4. Effect of marine omega-3 fatty acid supplementation on CRP levels in autoimmune diseases

Forest plot showing the overall and subgroup effects of marine omega-3 fatty acid supplementation compared with placebo on C-reactive protein (CRP) levels in rheumatoid arthritis, systemic lupus erythematosus, and psoriasis. Each square reflects the weight of an included study, and the diamond represents the pooled effect estimate.

Secondary Outcomes

Secondary outcomes were analyzed to assess the broader clinical and inflammatory effects of vitamin D and marine-derived omega-3 fatty acid supplementation across autoimmune diseases. These included patient-reported measures such as the Visual Analogue Scale (VAS) for pain, the Health Assessment Questionnaire (HAQ), and the Patient Global Assessment (PGA); inflammatory biomarkers including interleukin-6 (IL-6) and erythrocyte sedimentation rate (ESR); joint assessments such as Tender Joint Count (TJC) and Swollen Joint Count (SJC); and the disease-specific Psoriasis Area and Severity Index (PASI). Pooled effect sizes, 95% confidence intervals, p-values, and heterogeneity statistics are summarized in Table 3. Forest plots for these outcomes are presented in Figures 5–14 (see Supplementary Figures).

Although some secondary outcomes demonstrated statistical significance, these findings were derived from a limited number of studies (≤3) accompanied by moderate-to-high heterogeneity (I^2 ≥65%); they should therefore be interpreted cautiously, as they may be influenced by small-study effects or between-study variability. GRADE certainty assessment was not conducted for secondary outcomes owing to the limited number of studies (≤3), small sample sizes, and high risk of bias across studies, which restricted meaningful evaluation of evidence certainty.

Table 3. Pooled Effects of Vitamin D and Marine-Derived Omega-3 Fatty Acid Supplementation on Secondary Clinical and Biomarker Outcomes in Autoimmune Diseases

Outcome	Disease	Intervention	Studies (n, Ref. No.)	Total N	SMD (95% CI)	p-value	I^2 (%)	Significant
VAS pain	RA	Vitamin D	3 [23, 24, 34]	316	-0.22 [-0.45, -0.00]	0.05	0%	Yes

Outcome	Disease	Intervention	Studies (n, Ref. No.)	Total N	SMD (95% CI)	p-value	I^2 (%)	Significant
HAQ	RA	Vitamin D	3 [17, 23, 24]	341	-0.11 [-0.40, 0.19]	0.48	29%	No
TJC	RA	Omega-3	2 [16, 28]	69	-1.59 [-2.73, -0.46]	0.006	70%	Yes
IL-6	RA	Omega-3	3 [16, 18, 31]	169	0.56 [0.02, 1.10]	0.04	65%	Yes
SJC	RA	Omega-3	2 [16, 28]	69	-2.64 [-6.84, 1.56]	0.22	95%	No
VAS pain	RA	Omega-3	2 [16, 31]	127	1.68 [-1.08, 4.43]	0.23	97%	No
HAQ	RA	Omega-3	2 [16, 31]	127	0.21 [-0.14, 0.56]	0.53	0%	No
PGA	RA	Omega-3	3 [16, 27, 31]	153	-0.08 [-0.40, 0.23]	0.60	0%	No
ESR	SLE	Omega-3	2 [21, 32]	92	-0.14 [-1.36, 1.09]	0.83	87%	No
PASI	Psoriasis	Vitamin D	2 [19, 25]	141	0.12 [-0.22, 0.47]	0.48	0%	No

Statistical significance was defined as $p < 0.05$. Abbreviations: RA, Rheumatoid Arthritis; SLE, Systemic Lupus Erythematosus; PASI, Psoriasis Area and Severity Index; HAQ, Health Assessment Questionnaire; VAS, Visual Analogue Scale; TJC, Tender Joint Count; SJC, Swollen Joint Count; PGA, Patient Global Assessment; IL-6, Interleukin-6; ESR, Erythrocyte Sedimentation Rate; SMD, Standardized Mean Difference; CI, Confidence Interval.

Funnel Plots and Reporting Biases

The funnel plot for the meta-analysis of vitamin D supplementation on CRP levels in autoimmune-disease subgroups (Figure 15a) shows a broadly symmetrical distribution of included studies around the pooled effect size (SMD), with most studies concentrated near the null-effect line and higher-precision studies clustered toward the top. Because fewer than ten studies were included, funnel plots are not considered reliable for detecting publication bias and should be interpreted cautiously; although rheumatoid-arthritis studies predominate, the observed symmetry supports the reliability of the pooled findings.

In contrast, the funnel plot for marine-derived omega-3 fatty acid supplementation on CRP levels in autoimmune disorders (Figure 15b) displays a mildly asymmetrical pattern, with a broad spread of studies, predominantly those investigating rheumatoid arthritis. The pooled effect is centered near the null value (SMD = 0), yet a slight rightward skew may indicate potential small-study effects or mild publication bias favoring studies reporting positive effects. Psoriasis is represented by a single study, and no eligible study was available for SLE. Given the limited number of included studies, a formal test for funnel-plot asymmetry (e.g., Egger's test) was not performed, as such tests lack statistical power with fewer than ten studies; findings from this plot should therefore be interpreted with appropriate caution.

Funnel plots were generated exclusively for the primary outcomes, as too few studies contributed to secondary-outcome analyses to allow meaningful interpretation of publication bias. No sensitivity analyses were conducted in this review owing to the limited number of included studies.

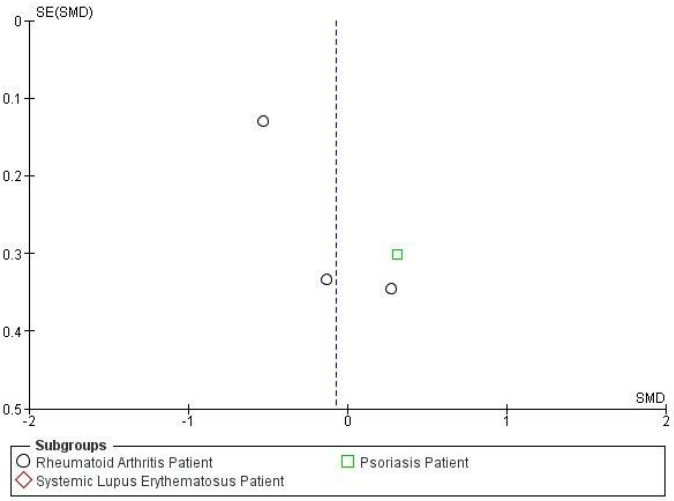

Figure 15a. Funnel plot – vitamin D supplementation and CRP

Funnel plot illustrating the distribution of studies assessing the effect of vitamin D supplementation versus placebo on CRP levels.

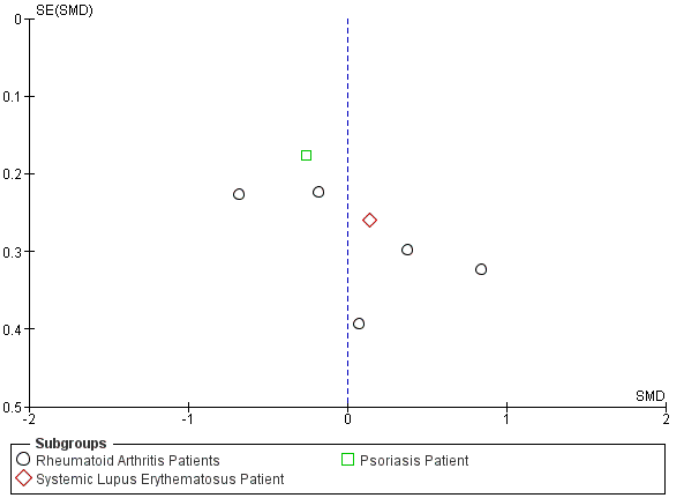

Figure 15b. Funnel plot – marine omega-3 fatty acid supplementation and CRP

Funnel plot illustrating the distribution of studies assessing the effect of omega-3 fatty acid supplementation versus placebo on CRP levels.

DISCUSSION

This meta-analysis is among the first, to our knowledge, to systematically compare the effects of vitamin D and marine omega-3 fatty acid supplementation on both inflammatory and clinical outcomes across autoimmune diseases, with a focus on RA, SLE, and psoriasis. It includes 19 RCTs evaluating changes in CRP level and disease-specific symptoms. While neither intervention demonstrated a statistically significant reduction in CRP, several secondary outcomes suggest possible symptom-specific benefits, particularly in RA. The Cochrane Risk of Bias assessment found two studies at low risk, seven at moderate risk, and ten at high risk of bias. Pooled analysis showed that vitamin D and omega-3 fatty acid supplementation had no statistically significant effect on CRP across autoimmune conditions; however, this should not be interpreted as definitive evidence of ineffectiveness. Pooled analyses of both interventions exhibited substantial heterogeneity ($I^2 > 65\%$), likely reflecting variability in intervention dosage, sample size,

treatment duration, baseline disease activity, intervention protocols, and population characteristics. In RA specifically, subgroup interpretation was limited by inconsistent dosing schedules and short intervention periods, often up to 12 weeks, with some variability ranging from 6 to 24 weeks. Data limitations in SLE and psoriasis further restricted subgroup analysis, constraining cross-disease comparability. The certainty of evidence across most outcomes ranged from low to very low, primarily owing to risk of bias, inconsistency, and imprecision; substantial heterogeneity ($I^2 > 60\%$ in several analyses) further limits the reliability and generalizability of the pooled estimates.

Among secondary outcomes, vitamin D supplementation significantly reduced pain scores (VAS) in RA patients but had no significant effect on functional status as measured by HAQ. Omega-3 supplementation in RA showed significant improvements in TJC and IL-6 levels, whereas SJC, HAQ, VAS pain, and PGA remained unaffected. Notably, the pooled analysis indicated a statistically significant effect on IL-6 levels, whereas individual studies showed inconsistent and largely non-significant results; this discrepancy may reflect increased statistical power in pooled analysis, differences in study weighting, and variability in baseline IL-6 levels across studies. Given the inconsistency and moderate heterogeneity, this finding should be interpreted with caution and not considered conclusive. Importantly, most individual trials did not demonstrate statistically significant effects, and pooled significance observed in some outcomes may reflect cumulative effects rather than consistent findings across studies.

For SLE, omega-3 supplementation did not significantly affect ESR. In psoriasis, vitamin D did not significantly alter PASI scores. No analysis was conducted for vitamin D in SLE or omega-3 in psoriasis owing to a lack of eligible data.

Several trials observed improvements in clinical symptoms such as pain and fatigue, highlighting the potential for broader effects of vitamin D and omega-3 supplementation beyond CRP reduction [35,36]; these outcomes warrant further investigation to fully characterize the therapeutic potential of these interventions. Chen et al. provided evidence that vitamin D treatment significantly reduced CRP levels in individuals with RA [37], and Dursun et al. found that vitamin D suppressed inflammatory biomarkers such as CRP and improved clinical outcomes in RA patients [38]. For SLE and psoriasis, our findings coincide with Beygi et al., who reported no significant effect of vitamin D supplementation on CRP levels in psoriasis patients [39]. Similarly, Huerta et al. concluded that omega-3 supplementation improved inflammatory markers, including CRP, in patients with psoriatic arthritis [40]; our analysis did not replicate this result, possibly owing to variability among included studies.

Despite null findings for the systemic inflammatory marker CRP, several clinically meaningful improvements were observed. Vitamin D significantly reduced pain levels in RA patients as measured by VAS, aligning with previous findings by Al-Saoodi et al., who reported symptom improvements and reductions in inflammatory markers [41]. Clinical studies have also shown that omega-3 supplementation can modulate disease activity in RA, including reductions in tender and swollen joint counts [42]. Regarding psoriasis, Formisano et al. found no significant changes in PASI scores after vitamin D supplementation over 3, 6, and 12 months, consistent with our results [43]. However, Jiao et al. reported that omega-3 supplementation significantly reduced ESR in SLE patients [44], in contrast to our findings; this discrepancy may reflect heterogeneity among the included studies, potentially arising from differing study parameters or patient populations, which can introduce inconsistency and affect pooled estimates. Additional well-designed, large-scale trials are required to better characterize

the specific effects of omega-3 fatty acids on ESR in the SLE population.

This systematic review and meta-analysis contributes novel insight by simultaneously evaluating biomarker- and symptom-based outcomes across multiple autoimmune diseases – an approach that broadens the scope of existing literature, which has typically concentrated on a single intervention or disease. However, our findings are constrained by heterogeneity, small sample sizes, and limited representation of non-RA conditions. Subgroup analysis was conducted for CRP, but insufficient study data prevented similar stratification for other outcomes.

STRENGTHS AND LIMITATIONS

This meta-analysis was conducted using a rigorous and systematic methodology in accordance with PRISMA guidelines, enabling a comprehensive evaluation of the effects of vitamin D and marine-derived omega-3 fatty acid interventions on CRP levels in autoimmune diseases. Incorporating secondary outcomes, such as inflammatory markers and clinical symptoms, adds depth to the analysis and broadens understanding of the potential therapeutic effects of these interventions. The significant decrease in VAS pain score, together with improvement in TJC among patients receiving vitamin D, highlights the clinical relevance of the findings for the management of RA. While individual trials often reported non-significant findings, this meta-analysis provides a quantitative synthesis that confirms the lack of a consistent effect across studies and allows estimation of overall trends; nonetheless, the absence of strong effects across individual trials reinforces the need for cautious interpretation of pooled results.

Notable limitations include variability in population characteristics, dosages, and supplementation duration across the included studies, which influenced heterogeneity among the results. Evaluation of long-term effects, particularly in SLE, is further constrained by varied study quality and relatively short follow-up durations. In some cases, original data were unavailable and had to be transformed using established formulas into approximate means and standard deviations from medians or other statistical parameters, which may introduce minor estimation error; adherence to standardized conversion methods minimizes this risk and helps ensure the robustness of the overall conclusions.

CONCLUSION

In conclusion, current evidence does not provide strong support for the effectiveness of vitamin D or marine-derived omega-3 fatty acid supplementation in reducing systemic inflammation in autoimmune diseases. Although some improvements were observed in selected clinical outcomes, particularly in rheumatoid arthritis, these findings are based on limited evidence and should be interpreted with caution. Substantial heterogeneity and variability across studies further limit the generalizability of the results. Future large-scale, well-designed randomized controlled trials are required to establish the clinical efficacy of vitamin D and marine-derived omega-3 fatty acid supplementation in autoimmune conditions.

LIST OF ABBREVIATIONS

RA: Rheumatoid Arthritis

SLE: Systemic Lupus Erythematosus

PsA: Psoriatic Arthritis

eRA: early Rheumatoid Arthritis

IU: International Unit

ACR: American College of Rheumatology

ARA: American Rheumatism Association

EULAR: European Alliance of Associations for Rheumatology

O3FA: Omega-3 Fatty Acid

MTX: Methotrexate

DMARDS: Disease-Modifying Anti-Rheumatic Drugs

DHA: Docosahexaenoic Acid

EPA: Eicosapentaenoic Acid

HsCRP: High-Sensitivity C-Reactive Protein

ESR: Erythrocyte Sedimentation Rate

VAS: Visual Analogue Scale

PGA/PatGA: Patient Global Assessment

PhyGA: Physician's Global Assessment

HAQ-DI: Health Assessment Questionnaire-Disability Index

IL-6: Interleukin-6

TNF: Tumor Necrosis Factor

PASI: Psoriasis Area and Severity Index

SLEDAI: Systemic Lupus Erythematosus Disease Activity Index

DAS: Disease Activity Score

FSS: Fatigue Severity Scale

ELISA: Enzyme-Linked Immunosorbent Assay

TJC: Tender Joint Count

SJC: Swollen Joint Count

ECM: Extracellular Matrix

SLAM-R: Systemic Lupus Erythematosus Activity Measure–Revised

dsDNA: Double-Stranded Deoxyribonucleic Acid

sRANKL: Soluble Receptor Activator of Nuclear Factor Kappa-B Ligand

IQR: Inter-Quartile Range

SMD: Standard Mean Difference

SEM: Standard Error of the Mean

CI: Confidence Interval

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Contributors

YA conceived and designed the review and developed the methodology. AA and UA performed the literature search, study selection, data extraction, and formal analysis, and drafted the manuscript. MKK contributed to data validation and investigation. SA performed formal analysis, visualization, and data curation. MS contributed to investigation and critically revised the manuscript for important intellectual content. ST provided resources and critically revised the manuscript. HNT supervised the study. All authors read and approved the final manuscript and agree to be accountable for all aspects of the work.

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Competing interests

None declared.

Ethical consideration

Not applicable. This systematic review and meta-analysis is based on previously published trial data; no human subjects were directly involved in this study.

Data availability statement

The datasets analyzed in the current study are available from the corresponding author upon reasonable request.

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