Oftalmologi: Jurnal Kesehatan Mata Indonesia 2025, Volume 7, Number 3.
P-ISSN. 2723-6935, E-ISSN. 2541-4283
Received: 27 September 2025; Revised: 24 December 2025; Accepted: 24 December 2025

Omega-3 Fatty Acids for Dry Eye Disease: An Updated Systematic Review

Gusti Ayu Ning Wikan Sari[1], Daniel Atnil[2], Thessia Eflien Pelupessy[3]
[1]*Kembangan Regional General Hospital, Jakarta Barat, Indonesia*
[2]*Faculty of Medicine, Pelita Harapan University, Tangerang, Indonesia*
[3]*Masohi Regional General Hospital, Maluku Tengah, Indonesia*
**Correspondence: Gusti Ayu Ning Wikan Sari, wikan.sari9@gmail.com*

How to Cite:
Sari, G. A. N. W., Atnil, D., & Pelupessy, T. E. (2025). Omega-3 Fatty Acids for Dry Eye Disease: An Updated Systematic Review. *Oftalmologi: Jurnal Kesehatan Mata Indonesia*, *7*(3), 105–117.
https://doi.org/10.11594/ojkmi.v7i3.94

ABSTRACT
Introduction: Dry eye disease (DED) is a multifactorial disorder involving tear film instability and ocular surface inflammation. Oral omega-3 fatty acids have been investigated as adjunctive therapy due to their anti-inflammatory and tear-stabilizing effects.
Methods: This systematic review followed PRISMA guidelines and included randomized controlled trials and prospective studies published up to August 2025. Databases searched were PubMed, Scopus, Web of Science, and the Cochrane Library. Primary outcomes were tear break-up time and patient-reported symptoms, with secondary outcomes including Schirmer test results, ocular surface staining, inflammatory markers, and adverse events.
Results: Fifteen studies across various DED subtypes were included. Most reported improvements in tear film stability and symptoms, although two large trials found no significant benefit. Omega-3 supplementation was generally safe, with mild gastrointestinal effects.
Conclusion: Oral omega-3 supplementation is safe and shows moderate efficacy as an adjunctive therapy for dry eye disease, particularly in patients with tear film instability and ocular surface inflammation. Variability in outcomes across studies highlights the need for standardized formulations, optimal dosing regimens, and subgroup-specific recommendations in future trials.
Keywords: dry eye disease, ocular surface, omega-3 fatty acids, supplementation, tear film

ABSTRAK
Pendahuluan: Penyakit mata kering (dry eye disease/DED) merupakan gangguan multifaktorial yang ditandai oleh ketidakstabilan lapisan air mata dan peradangan permukaan okular. Asam lemak omega-3 oral telah diteliti sebagai terapi tambahan karena efek antiinflamasi dan kemampuannya dalam menstabilkan lapisan air mata.
Metode: Tinjauan sistematis ini mengikuti pedoman PRISMA dan mencakup uji klinis teracak serta studi prospektif yang dipublikasikan hingga Agustus 2025. Pencarian dilakukan melalui PubMed, Scopus, Web of Science, dan Cochrane Library. Luaran utama meliputi waktu pecah lapisan air mata dan gejala yang dilaporkan pasien, sedangkan luaran sekunder mencakup uji Schirmer, pewarnaan permukaan okular, penanda inflamasi, dan kejadian efek samping.
Hasil: Lima belas studi dari berbagai subtipe DED dianalisis. Sebagian besar menunjukkan perbaikan stabilitas lapisan air mata dan gejala, meskipun dua studi besar tidak menemukan manfaat bermakna. Suplementasi omega-3 umumnya aman dengan efek samping gastrointestinal ringan.
Kesimpulan: Suplementasi omega-3 oral aman dan menunjukkan efektivitas sedang sebagai terapi tambahan DED. Variasi hasil antarstudi menegaskan perlunya standarisasi formulasi, dosis optimal, dan rekomendasi spesifik subkelompok pada penelitian mendatang.
Kata kunci: asam lemak omega-3, film air mata, mata kering, permukaan okular, suplementasi

INTRODUCTION

Dry Eye Disease (DED) is a multifactorial disorder of the ocular surface characterized by tear film instability, ocular discomfort, and fluctuating vision, which can significantly reduce quality of life. Its prevalence continues to rise worldwide due to aging populations, hormonal influences, and environmental exposures.[1,2] Omega-3 polyunsaturated fatty acids (PUFAs), primarily derived from fish oil, are known for their anti-inflammatory and immunomodulatory effects.[3,4] Inadequate dietary intake of omega-3 has been linked to meibomian gland dysfunction and tear film instability.[5,6]

Clinical trials have reported that omega-3 supplementation can improve tear film stability and patient symptoms.[7-9] However, larger multicenter studies such as the DREAM trial demonstrated inconsistent results regarding its efficacy.[10,11] Given these conflicting findings, systematic reviews highlight the need for further well-designed trials to clarify the role of omega-3 supplementation in DED management.[4] Current expert consensus, including TFOS DEWS II and professional guidelines, recommend omega-3 only as an adjunctive option rather than a primary therapy.[2,12,13]

METHODS

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Literature searches were performed in PubMed, Scopus, Web of Science, and Cochrane Library, from 2010 up to 2025. The research question was structured using the PICO framework: population (patients with DED, including MGD, contact lens wearers, post-LASIK, diabetes, rosacea, and post-cataract), intervention (oral omega-3 supplementation), comparator (placebo or standard treatment), and outcomes (symptom scores, TBUT, Schirmer test, ocular surface staining, and inflammatory biomarkers). Randomized controlled trials and prospective studies were eligible for inclusion. Three reviewers independently screened records, extracted data, and assessed methodological quality. Risk of bias was evaluated using the Cochrane RoB 2 tool for RCTs and ROBINS-I for non-randomized studies. Discrepancies were resolved through discussion and consensus.

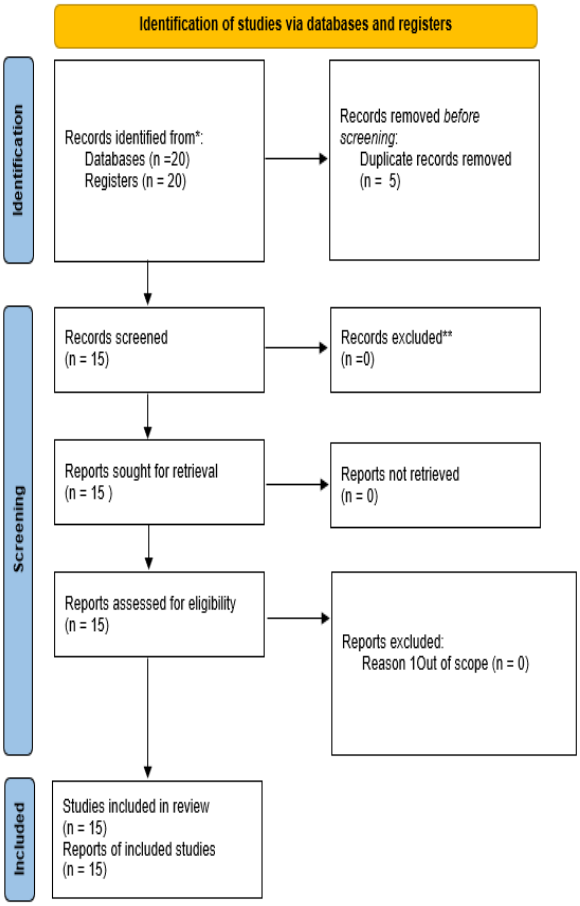

Figure 1. Prisma Flowchart

RESULT

A total of 15 studies were included, encompassing general DED patients, meibomian gland dysfunction (MGD), contact lens wearers, LASIK-associated DED, diabetes, rosacea, and post-cataract populations. In general DED, several RCTs reported significant improvement in TBUT, Schirmer scores, and OSDI following oral omega-3 supplementation.[5,7,14] Krill oil demonstrated superior anti-inflammatory effects compared to fish oil, reducing IL-

17A and improving tear osmolarity.[14] However, the DREAM extension study[10] and rTG omega-3 trials[15,16] showed no significant differences from placebo.

Among contact lens wearers, Bhargava & Kumar (2015)[8] found that six months of supplementation improved TBUT, Schirmer scores, and lens comfort, while a pilot trial also suggested benefit with minimal adverse events.[17] For LASIK-associated DED, omega-3 increased Schirmer scores and reduced staining, though TBUT and OSDI remained unchanged.[18] In diabetic patients, supplementation improved TBUT, Schirmer, OSDI, and conjunctival cytology.[9] In rosacea, omega-3 reduced ocular symptoms and surface inflammation.[19] Post-cataract surgery patients receiving omega-3 showed improved TBUT and tear stability.[20] Across studies, supplementation consistently reduced ocular surface inflammation, including decreased lid margin inflammation and HLA-DR expression.[21] Adverse events were minimal, and safety was confirmed in larger trials.[11,14]

The fifteen included studies were predominantly randomized controlled trials evaluating oral omega-3 supplementation in patients with dry eye disease (DED) and related subtypes, including meibomian gland dysfunction, contact lens–related DED, post-LASIK DED, rosacea-associated DED, and diabetes-related DED. Interventions consisted mainly of EPA and DHA in fish oil, krill oil, or re-esterified triglyceride formulations, with daily doses ranging from approximately 600 to 3000 mg and follow-up periods between 4 weeks and 12 months. Outcomes commonly assessed were symptom scores (OSDI, DESS, or VAS) and objective measures such as tear break-up time, Schirmer test, ocular surface staining, tear osmolarity, and inflammatory biomarkers. Participants were mostly middle-aged to older adults, with sample sizes ranging from 12 to over 500, and both sexes were represented, although several studies did not report detailed sex distributions. Diagnostic definitions of DED were generally based on a combination of symptoms and at least one abnormal objective test (for example OSDI above threshold, TBUT less than 10 seconds, Schirmer test 10 mm or less, or positive ocular surface staining), with some trials focusing on specific clinical phenotypes such as MGD or contact lens intolerance.

The large DREAM trial differed from many smaller studies in enrolling a broad, heterogeneous DED population, using a high-dose fish oil formulation (3000 mg/day EPA+DHA) with olive oil placebo, and applying stringent outcome definitions over a long follow-up, which may have diluted effects in subgroups more likely to benefit, such as patients with prominent inflammatory or evaporative disease. In contrast, several smaller trials targeted specific phenotypes, used different formulations (including krill oil), and had shorter follow-up, potentially increasing the likelihood of detecting benefit. Using the GRADE framework, the overall certainty of evidence for symptom improvement and TBUT was rated as moderate, downgraded for inconsistency and risk of bias, while evidence for Schirmer test and inflammatory outcomes was low. From a practical perspective, omega-3 supplements are generally affordable and widely available, but in low- and middle-income countries cost, product quality, and regulatory variability may limit access to high-dose or purified formulations. Therefore, while omega-3 may represent a feasible adjunctive option, its use should be balanced against local availability, patient affordability, and the modest certainty of benefit.

Table 1. Literature Review

No	Author, Year	Design	Intervention	Outcomes
1	Asbell et al., 2018 (DREAM)[11]	Multicenter RCT, double-blind, placebo-controlled (535 DED patients)	3000 mg/day EPA + DHA vs olive oil placebo, 12 mo	OSDI (primary), TBUT, Schirmer, staining
2	Hussain et al., 2020 (DREAM extension)[10]	Multicenter RCT, randomized withdrawal, double-blind (43 DED patients)	Continue omega-3 (3000 mg/day) vs switch to placebo, 12 mo	OSDI, staining, TBUT, Schirmer
3	Bhargava & Kumar, 2015[8]	Multicenter RCT, double-blind, placebo-controlled (496 contact lens wearers)	Omega-3 (EPA + DHA 600 mg bid) vs corn oil placebo, 6 mo	DESS (primary), Schirmer, TBUT, cytology
4	Bhargava et al., 2016[22]	Multicenter RCT, double-blind, placebo-controlled (130 rosacea + DED patients)	Omega-3 (EPA 720 mg + DHA 480 mg/day) vs olive oil placebo, 6 mo	DESS (primary), MGS, Schirmer, TBUT
5	Deinema et al., 2017[14]	RCT, double-masked, placebo-controlled (60 DED patients)	Fish oil (1000 mg EPA + 500 mg DHA/day) vs Krill oil (945 mg EPA + 510 mg DHA/day) vs olive oil placebo, 3 mo	OSDI, tear osmolarity, TBUT, cytokines
6	Goyal et al., 2017[18]	RCT, open-label randomized (60 LASIK patients)	Omega-3 (EPA 720 mg + DHA 480 mg/day) vs vit 400 mg, 12 wk, peri-LASIK	Schirmer (primary), TBUT, OSDI, staining
7	Jo & Lee, 2021[23]	RCT, double-masked, placebo-controlled (50 DED+MGD patients)	rTG ω-3 (600 mg EPA + 1640 mg DHA/day) vs olive oil placebo, 8 wk	OSDI, TBUT, staining, MGD score, strip meniscometry
8	Kangari et al., 2013[24]	RCT, double-blind, placebo-controlled (64 DED patients)	Omega-3 (180 mg EPA + 120 mg DHA bid) vs MCT placebo, 30 d	TBUT (primary), OSDI, Schirmer
9	Kawakita et al., 2013[25]	RCT, double-blind, placebo-controlled (27 DED patients)	Fish oil (EPA 1245 mg + DHA 540 mg/day) vs MCT placebo, 12 wk	VAS (dryness)/pain), TBUT, Schirmer, staining
10	Olenik et al., 2013[26]	RCT, double-blind, placebo-controlled (61 MGD patients)	Brudyse® (1.5 g/day, DHA 350 mg + EPA 42.5 mg + antioxidants) + lid hygiene vs placebo oil + lid hygiene, 3 mo	TBUT, OSDI, Schirmer, staining, MG expression
11	Wojtowicz et al., 2011[17]	Pilot RCT, double-masked, placebo-controlled (36 MGD patients)	TheraTears Nutrition (fish oil 450 mg EPA + 300 mg DHA + flaxseed oil) vs wheat germ oil placebo, 90 days	OSDI, TBUT, Schirmer, staining, evaprometry, meibum lipid composition
12	Eom et al., 2024[15]	Multicenter RCT, double-masked, placebo-controlled (132 DED+MGD patients)	rTG ω-3 (1680 mg EPA + 560 mg DHA/day) vs grape-seed oil placebo, 12 wk	OSDI (primary), NEI-VFQ-25, TBUT, staining, MMP-9, MG dropout
13	Georgakopoulos et al., 2016[9]	Prospective, non-randomized, single-arm (36 type 2 diabetes + DED patients)	Omega-3 (EPA 510 mg + DHA 345 mg/day), 3 mo	OSDI, TBUT, Schirmer, impression cytology

14	Bhargava et al., 201327	Prospective, interventional, placebo-controlled, double-blind randomized trial (264 DED patients)	Omega-3 fatty acids (500 mg capsule: 325 mg EPA + 175 mg DHA) twice daily for 3 months vs placebo	- 65% of omega-3 group vs 33% of placebo group showed symptom improvement (P=0.005) - TBUT significantly increased in omega-3 group (mean 2.54 ± 2.34 vs 0.13 ± 0.16) - Symptom score reduction: omega-3 2.02 ± 0.96 vs placebo 0.48 ± 0.22 (P<0.001) - Schirmer test slightly increased but did not correlate well with symptom improvement More pronounced effect in patients with blepharitis/meibomian gland disease
15	Chinnery et al., 2017[28]	Prospective, comparative pilot study; subset of randomized, double-masked, placebo-controlled trial (12 moderate DED patients)	Omega-3 EFAs (~1000 mg/day EPA + ~500 mg/day DHA) for 90 days vs placebo (olive oil 1500 mg/day)	- Greater reduction in OSDI score in omega-3 group (15.6 ± 2.8 vs 2.8 ± 4.1 units, p=0.04) - Greater reduction in tear osmolarity (22.63 ± 5.7 vs 2.7 mOsmol/L, p=0.04) - Corneal total nerve branch density (CTBD) higher in omega-3 (91.1 ± 8.6 vs 45.1 ± 13.4 branches/mm², p=0.004) - Corneal nerve branch density (CNBD) higher in omega-3 (63.4 ± 6.5 vs 27.9 ± 11.5 branches/mm², p=0.03) - Corneal nerve fiber length (CNFL) increased in omega-3 group (+2.9 ± 1.6 mm/mm², p=0.01) - Negative correlation between CTBD and tear osmolarity (r=0.70, p=0.01) - No significant changes in basal epithelial or corneal dendritic cell density

**DED: dry eye disease; MGD: Meibomian Gland Dysfunction; Mo: months; wk: weeks*

Risk of Bias

Table 2. Risk of Bias Result

No	Author, Year	Risk of Bias Tool	Overall Judgment
1	Asbell et al., 2018	RoB 2	Low to Some concerns
2	Hussain et al., 2020	RoB 2	Low risk
3	Bhargava & Kumar, 2015	RoB 2	Some concerns
4	Deinema et al., 2017	RoB 2	Low to Some concerns
5	Goyal et al., 2017	RoB 2	High risk
6	Jo & Lee, 2021	RoB 2	Low to Some concerns
7	Kangari et al., 2013	RoB 2	Low to Some concerns
8	Kawakita et al., 2013	RoB 2	Some concerns
9	Olenik et al., 2013	RoB 2	Some concerns
10	Wojtowicz et al., 2011	RoB 2	Some concerns
11	Eom et al., 2024	RoB 2	Some concerns
12	Georgakopoulos et al., 2016	ROBINS-I	Serious risk
13	Bhargava et al., 2013	RoB 2	Low Risk
14	Chinnery et al., 2017	Rob 2	Some Concerns
15	Bhargava R et al., 2016	Rob 2	Low Risk

Overall effects of omega-3 supplementation in dry eye disease Across the fifteen included randomized and prospective studies, oral omega-3 fatty acid supplementation demonstrated beneficial effects in patients with dry eye disease across diverse populations, including general DED, meibomian gland dysfunction, contact lens wearers, diabetes-associated DED, LASIK-associated DED, and rosacea-related DED, as summarized in Table 1. Most studies reported improvements in tear film stability measured by tear break-up time, tear production assessed by the Schirmer test, and patient-reported symptom scores such as OSDI and DESS. Improvements in ocular surface inflammation, including reduced lid margin inflammation, better meibomian gland expression, and decreased inflammatory mediators, were also observed in several trials.

In particular, Kangari et al. (2013) reported significant increases in TBUT and Schirmer scores and improvements in OSDI after 30 days of supplementation with 180 mg EPA plus 120 mg DHA twice daily in patients with DED. Oleñik et al. (2013) demonstrated improvements in TBUT, OSDI, lid margin inflammation, and meibomian gland expression in patients with MGD after three months of omega-3 supplementation. Deinema et al. (2017) showed that krill oil reduced IL-17A levels and improved tear osmolarity and TBUT more effectively than fish oil or placebo. However, not all studies demonstrated benefit. The large multicenter DREAM trial and its extension did not show significant differences between omega-3 supplementation and placebo in primary or secondary outcomes, including OSDI, TBUT, and Schirmer test values. Similarly, the re-esterified triglyceride omega-3 randomized trial in patients with DED and MGD did not find significant improvements over placebo. These neutral findings contrast with the positive results reported in several smaller trials.

Effects in specific DED subgroups in LASIK-associated DED, Goyal et al. (2017) reported that omega-3 supplementation significantly increased Schirmer scores and reduced conjunctival staining but did not significantly improve TBUT or OSDI. In patients with type 2 diabetes and DED, Georgakopoulos et al. (2017) observed improvements in TBUT, Schirmer test

values, OSDI scores, and conjunctival impression cytology after three months of omega-3 supplementation. In rosacea-related DED and MGD, Bhargava et al. reported significant improvements in symptom scores, meibomian gland secretion, TBUT, and Schirmer test values following omega-3 supplementation. Postoperative settings also showed benefit, with studies reporting improved tear stability after ocular surgery in patients receiving fatty acid supplementation. Among contact lens wearers, Bhargava and Kumar (2015) reported that six months of oral omega-3 supplementation significantly increased TBUT and Schirmer scores and improved dry eye symptoms and lens comfort in a large cohort of 496 participants. Wojtowicz et al. (2011) also reported improvements in tear film stability and symptom scores in contact lens users receiving omega-3 supplementation. Overall, contact lens–related DED consistently showed improvements in both subjective comfort and objective tear parameters across the included studies.

Although most studies reported at least one significant improvement with omega-3 supplementation, considerable variability in outcomes was observed. While several randomized controlled trials demonstrated improvements in both symptoms and objective tear parameters, the largest multicenter trials failed to confirm these benefits. Differences in omega-3 formulation, including fish oil, krill oil, and re-esterified triglyceride forms, daily doses ranging from approximately 600 mg to 3000 mg of EPA and DHA, treatment durations from 4 weeks to 12 months, and heterogeneity in patient populations were reported across studies. Krill oil supplementation was associated with greater reductions in inflammatory markers and improvements in tear osmolarity and TBUT compared with fish oil in one randomized trial. In contrast, trials using re-esterified triglyceride omega-3 did not demonstrate significant benefit over placebo.

Safety and tolerability of oral omega-3 supplementation were reported in most included studies. Across trials, omega-3 was generally well tolerated, with no serious treatment-related adverse events reported. The most common adverse events were mild gastrointestinal symptoms, including fishy aftertaste, nausea, dyspepsia, diarrhea, and abdominal discomfort. In large trials such as the DREAM study and its extension, adverse event rates were comparable between omega-3 and placebo groups, and discontinuation due to adverse events was uncommon. No clinically significant bleeding events or laboratory abnormalities were reported. Overall, omega-3 supplementation at doses up to 3000 mg per day for durations up to 12 months demonstrated a favorable safety profile. In the DREAM trial and its extension, the incidence of adverse events was comparable between the omega-3 and placebo groups, with no significant differences in serious adverse events. Similarly, other randomized controlled trials reported no clinically meaningful changes in laboratory parameters or bleeding complications associated with omega-3 supplementation. Discontinuation due to adverse events was rare and occurred at similar rates in intervention and placebo groups.

Overall, the safety data from the included studies indicate that oral omega-3 supplementation, at doses ranging from approximately 600 mg to 3000 mg of EPA and DHA per day and for durations up to 12 months, has a favorable safety profile in patients with dry eye disease.

A total of fifteen studies were included in this systematic review. The main characteristics of the included studies, including study design, population, intervention, and reported outcomes, are summarized in Table 1. Most studies were

randomized controlled trials with double-blind and placebo-controlled designs, involving patients with general dry eye disease, meibomian gland dysfunction, contact lens–related dry eye, post-LASIK dry eye, rosacea-associated dry eye, diabetes-related dry eye, and post-cataract surgery dry eye. The daily dose of omega-3 supplementation varied across studies, ranging from approximately 600 mg to 3000 mg of combined EPA and DHA, with intervention durations between 4 weeks and 12 months. The most commonly assessed outcomes were symptom scores using OSDI or DESS, tear break-up time, Schirmer test, and ocular surface staining.

As shown in Table 1, symptom improvement assessed by OSDI, DESS, or visual analog scale was reported in the majority of studies, including those by Bhargava and Kumar, Bhargava et al., Kangari et al., Olenik et al., Wojtowicz et al., Eom et al., Chinnery et al., and the prospective study in diabetic patients by Georgakopoulos et al. Improvements in tear film stability measured by tear break-up time were also frequently observed across studies, including contact lens wearers, patients with meibomian gland dysfunction, and post-refractive surgery patients. Several studies additionally demonstrated improvements in Schirmer test values and ocular surface staining. Anti-inflammatory effects, such as reductions in tear cytokines, matrix metalloproteinase-9, or tear osmolarity, were reported in studies by Deinema et al., Eom et al., and Chinnery et al., as detailed in Table 1.

In contrast, two large randomized trials, namely the DREAM study by Asbell et al. and its extension by Hussain et al., as summarized in Table 1, did not show significant differences between omega-3 supplementation and placebo in primary or secondary outcomes, including OSDI scores and objective tear parameters. Similarly, the re-esterified triglyceride omega-3 trial by Jo and Lee reported no significant benefit over placebo in patients with dry eye disease and meibomian gland dysfunction.

Overall, most of the included studies reported at least one significant improvement in either subjective symptoms or objective tear parameters with omega-3 supplementation, although the magnitude and consistency of effects varied among different populations and study designs, as presented in Table 1. The risk of bias assessment of the included studies is presented in Table 3. Using the RoB 2 tool for randomized controlled trials, most studies were judged as having low risk of bias or some concerns. Two trials, including those by Bhargava et al. (2013) and Bhargava R et al. (2016), were assessed as having low risk of bias. One study by Goyal et al. was judged to have a high risk of bias due to concerns in randomization and outcome assessment. The non-randomized prospective study by Georgakopoulos et al. was evaluated using ROBINS-I and was judged to have a serious risk of bias. Overall, the quality of evidence ranged from low risk to some concerns for most trials, with a limited number of studies showing high or serious risk, as summarized in Table 2.

Among the twelve randomized controlled trials evaluated with the Cochrane Risk of Bias 2 (RoB 2) tool, most were judged as *low risk* or *some concerns*, indicating varying levels of potential bias but not invalidating the overall findings. Only one study assessing LASIK-associated dry eye was rated as *high risk of bias*, primarily due to methodological limitations such as randomization and masking. The single non-randomized study included in this review was assessed using the ROBINS-I tool and judged to have a *serious risk of bias*, particularly in domains of confounding and participant selection. Overall, most studies demonstrated low to moderate risk of bias, supporting the general reliability of the evidence base. Nonetheless, results

from studies with higher or serious risk should be interpreted cautiously in the context of clinical recommendations.

DISCUSSION

This systematic review of fifteen randomized and prospective trials demonstrates that oral omega-3 fatty acids may provide beneficial effects in patients with Dry Eye Disease (DED) across diverse populations, including those with meibomian gland dysfunction (MGD), contact lens wearers, diabetic patients, LASIK-associated DED, and rosacea-related DED. Most studies reported improvements in tear film stability (TBUT), tear production (Schirmer test), and patient-reported symptoms such as OSDI and DESS.[14,16,23] Omega-3 supplementation also appeared to reduce ocular surface inflammation, including lid margin inflammation, improved meibomian gland expression, and decreased inflammatory mediators such as IL-17A in krill oil trials.[14]

Despite these findings, the certainty of evidence is limited by methodological considerations. Most randomized trials were rated as *some concerns* in risk of bias, particularly in outcome measurement domains. The DREAM extension trial, while relatively well-designed, did not demonstrate significant benefit over placebo,[10] in contrast to smaller studies that reported improvement.[8,24] Non-randomized studies, such as Georgakopoulos (2017),[9] were judged to be at serious risk of bias, providing only supportive, low-certainty evidence. Consequently, the overall certainty of the body of evidence, as evaluated using the GRADE framework, was downgraded from high to moderate or low.[3,4]

1. Omega-3 Effects in General DED Populations

Oral omega-3 supplementation demonstrated beneficial effects in general DED populations, including patients with meibomian gland dysfunction (MGD), rosacea-related DED, LASIK-associated DED, and diabetes-associated DED. Kangari et al. (2013)[24] reported that 180 mg EPA plus 120 mg DHA twice daily for 30 days significantly increased TBUT, Schirmer scores, and improved OSDI in patients aged 45–90 years with DED. Similarly, Oleñik et al. (2013)[26] found that omega-3 supplementation in patients with MGD improved TBUT, OSDI, lid margin inflammation, and meibomian gland expression after three months of treatment.

Anti-inflammatory effects were particularly notable with krill oil. Deinema et al. (2017)[14] demonstrated that krill oil decreased IL-17A levels and improved tear osmolarity and TBUT more effectively than fish oil. Krill-derived omega-3 may offer superior bioavailability and anti-inflammatory effects. In contrast, large multicenter studies such as the DREAM extension trial and the rTG omega-3 randomized clinical trial did not show significant improvements in TBUT, Schirmer scores, or OSDI[10,15] highlighting variability in efficacy that may be influenced by formulation, dosage, or patient characteristics.

LASIK-associated and diabetes-related DED appear to respond differently to omega-3 supplementation. Goyal et al. (2017)[18] reported that in LASIK patients, omega-3 supplementation increased Schirmer scores and reduced conjunctival staining but did not significantly improve TBUT or OSDI. Georgakopoulos et al. (2017)[9] observed that in patients with type 2 diabetes, omega-3 supplementation improved TBUT, Schirmer test values, and OSDI, as well as conjunctival cytology, suggesting that baseline inflammation or systemic comorbidities may influence responsiveness. Beyond LASIK, benefits may also extend to cataract patients. Elaleem et al. (2022)[20] reported that oral linoleinic acid improved TBUT and tear stability after phacoemulsification,

supporting a role for supplementation in enhancing postoperative ocular surface recovery.

Variability in treatment response has been noted. While most RCTs support benefits, Bhargava et al. (2023)[19] highlighted that supplementation may be inconsistently effective, reflecting heterogeneity in patient populations and trial designs. Similarly, Byrne (2022)[6] concluded that evidence remains mixed when translated into clinical practice.

Overall, omega-3 supplementation in general DED populations appears to support tear film stability and reduce ocular surface inflammation. However, variability in outcomes underscores the importance of individualized treatment strategies based on DED subtype, severity, and baseline tear film characteristics.

2. Omega-3 Effects in Contact Lens–Related DED

In contact lens wearers, omega-3 supplementation has primarily been associated with improved lens comfort, tear production, and tear film stability. Bhargava and Kumar (2015)[8] reported that six months of oral omega-3 supplementation significantly increased TBUT and Schirmer scores, while enhancing lens comfort and reducing dry eye symptoms in a cohort of 496 contact lens users. These findings are consistent with earlier pilot work by Wojtowicz et al. (2011),[17] which suggested that omega-3 supplementation could improve tear film stability in contact lens users with dry eye. Systematic reviews have similarly recognized contact lens wearers as a subgroup that may benefit from omega-3 supplementation.[3] The TFOS DEWS II Management Report also highlights nutritional supplementation, including omega-3 fatty acids, as a supportive option for managing contact lens–related dry eye.[12]

The mechanisms underlying these improvements likely involve both tear film stabilization and anti-inflammatory effects. Omega-3 fatty acids have been shown to modify meibomian gland secretions, leading to a more stable lipid layer and enhanced lubrication under contact lenses. Whereas omega-3 use in general DED populations emphasizes symptom relief and reduction of ocular surface inflammation, in contact lens wearers the clinical emphasis is on functional outcomes such as lens tolerance and comfort. Variability in response among contact lens users may be influenced by lens material, wearing schedules, and baseline tear film characteristics. Although most studies have demonstrated positive outcomes, long-term studies and standardized dosing regimens remain limited. Bhargava and Kumar (2015)[8] observed that improvements plateaued after six months, suggesting a possible ceiling effect or the need for sustained supplementation to maintain benefits.

Omega-3 supplementation was generally safe in contact lens wearers, with minimal adverse effects reported.[8,17] Larger randomized trials have similarly confirmed the good safety profile of oral omega-3 supplementation in DED patients.[14] The TFOS DEWS II Management Report also emphasizes that omega-3 can be considered a safe and supportive adjunctive therapy, particularly when combined with standard measures such as artificial tears and lens hygiene.[12] Considering its beneficial impact on both tear film physiology and subjective comfort, omega-3 may therefore be a valuable addition to the management of contact lens–related DED.

3. Considerations and Safety

Despite overall benefits, variability in study outcomes warrants cautious interpretation. Large multicenter studies, including the DREAM extension and the rTG omega-3 randomized trial, did not demonstrate significant improvements in

TBUT, Schirmer scores, or OSDI compared with placebo.[10,15] These discrepancies may be attributable to differences in omega-3 formulation, dosage, treatment duration, or patient characteristics. Notably, krill oil consistently showed greater anti-inflammatory and symptomatic improvement than fish oil, suggesting that source and bioavailability are important determinants of efficacy.[14]

Molina-Leyva et al. (2020)[29] showed Mediterranean diet adherence improved dry eye parameters, and the TFOS Lifestyle Report emphasized nutrition and environmental factors in ocular surface health.[30] Safety data across included trials were consistently favorable. Minimal adverse events were reported even at higher doses, supporting the feasibility of long-term oral omega-3 supplementation in both general DED and contact lens populations.[8,16,24] This reinforces the potential for omega-3 as a safe adjunctive therapy.

CONCLUSION

Oral omega-3 fatty acids are generally safe and can provide moderate improvements in tear film stability, tear production, and symptom relief in patients with Dry Eye Disease across various populations. Krill oil and high-dose DHA/EPA formulations may offer superior anti-inflammatory and symptomatic benefits compared with standard fish oil. However, treatment response can vary depending on the DED subtype, baseline severity, formulation, and duration of therapy. Clinicians should consider these factors when recommending omega-3 supplementation, and further standardized studies are needed to optimize dosing and long-term outcomes.

REFERENCE

1. Stapleton F, Alves M, Bunya VY, Jalbert I, Lekhanont K, Malet F, et al. TFOS DEWS II Epidemiology Report. *Ocul Surf*. 2017 Jul;15(3):334–65. Available from: https://linkinghub.elsevier.com/retrieve/pii/S154201241730109X
2. Craig JP, Nichols KK, Akpek EK, Caffery B, Dua HS, Joo CK, et al. TFOS DEWS II Definition and Classification Report. *Ocul Surf*. 2017 Jul;15(3):276–83. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1542012417301192
3. Downie LE, Ng SM, Lindsley KB, Akpek EK. Omega-3 and omega-6 polyunsaturated fatty acids for dry eye disease. *Cochrane Database Syst Rev*. 2019 Dec 18. Available from: https://doi.org/10.1002/14651858.CD011016.pub2
4. O'Byrne C, O'Keeffe M. Omega-3 fatty acids in the management of dry eye disease—An updated systematic review and meta-analysis. *Acta Ophthalmol (Copenh)*. 2023 Mar;101(2). Available from: https://doi.org/10.1111/aos.15255
5. Wang WX, Ko ML. Efficacy of Omega-3 Intake in Managing Dry Eye Disease: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *J Clin Med*. 2023 Nov 10;12(22):7026. Available from: https://doi.org/10.3390/jcm12227026
6. Byrne R. Does omega-3 supplementation improve dry eye symptoms? *Evid-Based Pract*. 2022 Jan;25(1):37–8. Available from: https://doi.org/10.1097/EBP.0000000000001420
7. Christen WG, Cook NR, Manson JE, Buring JE, Lee IM, Bubes V, et al. Efficacy of Marine ω-3 Fatty Acid Supplementation vs Placebo in Reducing Incidence of Dry Eye Disease in Healthy US Adults: A Randomized Clinical Trial. *JAMA Ophthalmol*. 2022 Jul 1;140(7):707. Available from: https://doi.org/10.1001/jamaophthalmol.2022.2031
8. Bhargava R, Kumar P. Oral Omega-3 Fatty Acid Treatment for Dry Eye in Contact Lens Wearers. *Cornea*. 2015 Apr;34(4):413–20. Available from: https://doi.org/10.1097/ICO.0000000000000392
9. Georgakopoulos CD, Makri OE, Pagoulatos D, Vasilakis P, Peristeropoulou P, Kouli V, et al. Effect of Omega-3 Fatty Acids Dietary Supplementation on Ocular Surface and Tear Film in Diabetic Patients with Dry Eye. *J Am Coll Nutr*. 2017 Jan 2;36(1):38–43. Available from: https://doi.org/10.1080/07315724.2016.1170643
10. Hussain M, Shtein RM, Pistilli M, Maguire MG, Oydanich M, Asbell PA. The DREAM

extension study – A randomized clinical trial of withdrawal of supplementation with omega-3 fatty acid in patients with dry eye disease. *Ocul Surf*. 2020 Jan;18(1):47–55. Available from: https://doi.org/10.1016/j.jtos.2019.08.003
11. Asbell PA. n-3 Fatty Acid Supplementation for the Treatment of Dry Eye Disease. *N Engl J Med*. 2018 May 3;378(18):1681–90. Available from: https://doi.org/10.1056/NEJMoa1709691
12. Jones L, Downie LE, Korb D, Benitez-del-Castillo JM, Dana R, Deng SX, et al. TFOS DEWS II Management and Therapy Report. *Ocul Surf*. 2017 Jul;15(3):575–628. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1542012417301143
13. Amescua G, Ahmad S, Cheung AY, Choi DS, Jhanji V, Lin A, et al. Dry Eye Syndrome Preferred Practice Pattern®. *Ophthalmology*. 2024 Apr;131(4):P1–49. Available from: https://doi.org/10.1016/j.ophtha.2023.12.001
14. Deinema LA, Vingrys AJ, Wong CY, Jackson DC, Chinnery HR, Downie LE. A Randomized, Double-Masked, Placebo-Controlled Clinical Trial of Two Forms of Omega-3 Supplements for Treating Dry Eye Disease. *Ophthalmology*. 2017 Jan;124(1):43–52. Available from: https://doi.org/10.1016/j.ophtha.2016.09.015
15. Eom Y, Jun I, Jeon HS, Lim DH, Lee H, Hwang HS, et al. Re-Esterified Triglyceride ω-3 Fatty Acids in Dry Eye Disease With Meibomian Gland Dysfunction: A Randomized Clinical Trial. *JAMA Ophthalmol*. 2024 Jul 1;142(7):617. Available from: https://doi.org/10.1001/jamaophthalmol.2024.1816
16. Park J, Yoo YS, Shin E, Han G, Shin K, Lim DH, et al. Effects of the re-esterified triglyceride (rTG) form of omega-3 supplements on dry eye following cataract surgery. *Br J Ophthalmol*. 2021 Nov;105(11):1504–9. Available from: https://doi.org/10.1136/bjophthalmol-2020-317164
17. Wojtowicz JC, Butovich I, Uchiyama E, Aronowicz J, Agee S, McCulley JP. Pilot, Prospective, Randomized, Double-masked, Placebo-controlled Clinical Trial of an Omega-3 Supplement for Dry Eye. *Cornea*. 2011 Mar;30(3):308–14. Available from: https://doi.org/10.1097/ICO.0b013e3181e0c310
18. Goyal P, Jain AK, Malhotra C. Oral Omega-3 Fatty Acid Supplementation for Laser In Situ Keratomileusis–Associated Dry Eye. *Cornea*. 2017 Feb;36(2):169–75. Available from: https://doi.org/10.1097/ICO.0000000000001047
19. Bhargava R, Pandey K, Ranjan S, Mehta B, Malik A. Omega-3 fatty acids supplements for dry eye – Are they effective or ineffective? *Indian J Ophthalmol*. 2023 Apr;71(4):1619–25. Available from: https://doi.org/10.4103/IJO.IJO_2789_22
20. Abd Elaleem AE, Ahmed D, Saif M. Dry Eye Changes After Phacoemulsification After Using Oral Linoleinic Acid (Omega 3 Fatty Acids). *Egypt J Med Res*. 2022 Apr 1;3(2):196–212. Available from: https://ejmr.journals.ekb.eg/article_240113.html
21. Roy NS, Yu Y, Ying GS, Maguire MG, Asbell PA, for the DREAM Study Group. Effect of Omega-3 on HLA-DR Expression by Conjunctival Cells and Tear Cytokine Concentrations in the DREAM Study. *Eye Contact Lens Sci Clin Pract*. 2022 Sep;48(9):384–90. Available from: https://doi.org/10.1097/ICL.0000000000000916
22. Bhargava R, Chandra M, Bansal U, Singh D, Ranjan S, Sharma S. A Randomized Controlled Trial of Omega 3 Fatty Acids in Rosacea Patients with Dry Eye Symptoms. *Curr Eye Res*. 2016 Oct 2;41(10):1274–80. Available from: https://doi.org/10.3109/02713683.2015.1122810
23. Jo YJ. Effects of dietary high dose DHA omega-3 supplement in dry eye with meibomian gland dysfunction. *Int J Ophthalmol*. 2021 Nov 18;14(11):1700–6. Available from: http://ies.ijo.cn/gjyken/ch/reader/view_abstract.aspx?file_no=20211108&flag=1
24. Kangari H, Eftekhari MH, Sardari S, Hashemi H, Salamzadeh J, Ghassemi-Broumand M, et al. Short-term Consumption of Oral Omega-3 and Dry Eye Syndrome. *Ophthalmology*. 2013 Nov;120(11):2191–6. Available from: https://doi.org/10.1016/j.ophtha.2013.06.009
25. Kawakita T, Kawabata F, Tsuji T, Kawashima M, Shimmura S, Tsubota K. Effects of dietary supplementation with fish oil on dry eye syndrome subjects: randomized controlled trial. *Biomed Res*. 2013;34(5):215–20. Available from: https://doi.org/10.2220/biomedres.34.215

26. Oleñik A, Jiménez-Alfaro B, Alejandre A, Mahillo-Fernández I. A randomized, double-masked study to evaluate the effect of omega-3 fatty acids supplementation in meibomian gland dysfunction. *Clin Interv Aging*. 2013 Aug;8:1133–8. Available from: https://doi.org/10.2147/CIA.S44699
27. Bhargava R, Kumar P. A randomized controlled trial of omega-3 fatty acids in dry eye syndrome. *Int J Ophthalmol*. 2013;6(6):811–5.
28. Chinnery HR, Naranjo Golborne C, Downie LE. Omega-3 supplementation is neuroprotective to corneal nerves in dry eye disease: a pilot study. *Ophthalmic Physiol Opt*. 2017 Jul;37(4):473–81. Available from: https://doi.org/10.1111/opo.12365
29. Molina-Leyva I, Molina-Leyva A, Riquelme-Gallego B, Cano-Ibáñez N, García-Molina L, Bueno-Cavanillas A. Effectiveness of Mediterranean Diet Implementation in Dry Eye Parameters: A Study of PREDIMED-PLUS Trial. *Nutrients*. 2020 May 1;12(5):1289. Available from: https://doi.org/10.3390/nu12051289
30. Markoulli M, Ahmad S, Arcot J, Arita R, Benitez-del-Castillo J, Caffery B, et al. TFOS Lifestyle: Impact of nutrition on the ocular surface. *Ocul Surf*. 2023 Jul;29:226–71. Available from: https://doi.org/10.1016/j.jtos.2023.03.004