Headache Medicine 2026, 17(3):256-266 p-ISSN 2178-7468, e-ISSN 2763-6178

Headache Medicine

DOI: 10.48208/HeadacheMed.2026.35

Review

Efficacy of combined curcumin and omega-3 supplementation for migraine management: a systematic review of randomized controlled trials

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Edited by:
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Abstract

Introduction
Migraine is a disabling neurological disorder. Omega-3 fatty acids and nano-curcumin have been investigated as adjuncts to standard prophylaxis.

Objective
To evaluate the effects of combined omega-3 and nano-curcumin supplementation on migraine attack frequency, headache severity and headache duration in adults.

Methods
PubMed, Embase, Scopus, Web of Science and the Cochrane Library were searched from inception through October 2025 for randomized trials of combined omega-3 and curcumin supplementation in adults with migraine. Clinical outcomes were synthesized narratively. Outcome-specific risk of bias was assessed using RoB 2.

Results
Of 1,632 records identified, 14 reports were assessed at full text. Eight were excluded because PICO criteria were not met, leaving six included reports that do not establish six independent trials. The three assessed clinical outcomes had some concerns for risk of bias. In the clinical dataset reported by Abdolahi et al., attack frequency at two months was 0.62 versus 1.67, 1.82 and 2.22 attacks/week with combination therapy, omega-3, nano-curcumin and placebo, respectively (overall between-group P=0.009). Severity differed across the four groups (P=0.02), but superiority over either monotherapy was not established. Headache duration did not differ significantly between groups (P=0.64).

Conclusions
Combination supplementation was associated with lower attack frequency in the reported clinical dataset. Small samples, two-month follow-up and repeated reporting of participants limit the evidence. Independent trials are needed to establish comparative efficacy and long-term safety.

Keywords:
Migraine
Curcumin
Omega-3 fatty acids
Dietary supplements
Systematic review

Received: August 5th, 2026
Revised: September 16, 2026
Accepted: October 13, 2026

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Introduction

Migraine is a disabling neurological disorder characterized by recurrent headache, often accompanied by nausea and sensitivity to light and sound. Trigeminovascular signaling and neuroinflammatory pathways contribute to its pathophysiology and clinical burden (1–5).

Acute and preventive therapies are selected according to migraine burden, comorbidities and tolerability (3). Medication overuse remains an important concern (6). These considerations motivate research on adjuncts but do not justify replacing established migraine treatment with supplements.

Interest in adjunctive nutraceutical approaches reflects incomplete response or tolerability concerns with some preventive treatments (7). Omega-3 fatty acids can modulate inflammatory signaling and lipid mediators (8). Curcumin also has anti-inflammatory properties, although bioavailability and formulation differences complicate translation into clinical practice (9). These mechanisms provide a rationale for evaluating combined supplementation; they do not establish clinical synergy. Randomized trials have examined combined supplementation for migraine. This review evaluates its effects on migraine attack frequency, headache severity and headache duration.

Materials and methods

Reporting format

The review was registered in PROSPERO as CRD420251171554 on October 21, 2025, following first submission on October 18, 2025. Public record: https://www.crd.york.ac.uk/PROSPERO/view/CRD420251171554.

Focused question

In adults with migraine, does combining omega-3 and curcumin supplementation, compared with either monotherapy, placebo or other eligible comparators, reduce migraine attack frequency, severity or duration?

Population (P), intervention (I), comparison (C), outcome (O)

The review addressed adults with migraine receiving combined curcumin and omega-3 supplementation, compared with either monotherapy, placebo, another treatment or no treatment in randomized controlled trials. The principal clinical outcome was attack frequency; headache severity and duration were additional clinical outcomes. The included interventions were nano-curcumin and omega-3 as adjuncts to standard prophylaxis. The registered clinical outcomes named attack frequency/number and duration. Severity was not separately named in the registry and is treated here as an additional exploratory clinical outcome. Biomarkers are ancillary to trial linkage and methodological appraisal, not substitutes for patient-important outcomes.

Eligibility criteria

Eligible trials enrolled adults aged 18 years or older with migraine and evaluated combined curcumin and omega-3 supplementation against either monotherapy, placebo, another treatment or no treatment. Migraine attack frequency, headache severity and headache duration were the clinical outcomes of interest. Non-randomized studies, case reports, reviews, animal studies and in vitro studies were excluded. Companion biomarker publications from eligible trials were retained to clarify trial methods and report linkage, rather than counted as additional clinical comparisons.

Search strategy and study selection

PubMed, Embase, Scopus, Web of Science and the Cochrane Library were searched independently by two authors from database inception through October 2025. Search concepts included curcumin or nano-curcumin, omega-3 fatty acids, supplementation or combination therapy, migraine, and pain or headache reduction. The database-specific strategies are presented in Table 1. A total of 1,364 records were removed before screening: 666 duplicate records and 698 records marked ineligible by an automation tool. An author checked the 698 records against the eligibility criteria and confirmed their exclusion. Two authors independently screened titles and abstracts, including further abstract screening of records retained after the initial stage, and assessed retrieved full texts against the eligibility criteria. Disagreements were resolved through discussion with a third reviewer. The review team assessed the full texts of all included reports, including Soveyd and Honarvar. The original search strategies are provided in Supplementary section S3; counts are summarized in Table 1 and Figure 1.

Data extraction and narrative synthesis

Participant characteristics, intervention and comparator regimens, clinical outcomes and reported withdrawals were extracted into structured tables. Publications from the same trial were considered together, and repeated clinical results were counted once. A narrative synthesis was used because participant overlap and insufficient information about independent samples precluded meta-analysis. Biomarker results were not included in the clinical outcome synthesis. Within-group changes were distinguished from between-group comparisons; standard errors were retained as reported. Exploratory unadjusted two-month mean differences

Table 1. Historical search strategies and reported counts

Database	Historical query description	Records
PubMed	("curcumin"[Supplementary Concept] OR "curcumin"[All Fields] OR "curcumin"[MeSH Terms] OR "curcumins"[All Fields] OR "curcumine"[All Fields] OR "curcumins"[All Fields] OR "nano curcumin"[All Fields] OR ("fatty acids omega 3"[Supplementary Concept] OR "fatty acids omega 3"[All Fields] OR "omega 3"[All Fields] OR "fatty acids, omega 3"[MeSH Terms] OR ("fatty"[All Fields] AND "acids"[All Fields] AND "omega 3"[All Fields]) OR "omega-3 fatty acids"[All Fields]) OR ("fatty acids omega 3"[Supplementary Concept] OR "fatty acids omega 3"[All Fields] OR "omega 3 fatty acids"[All Fields] OR "fatty acids, omega 3"[MeSH Terms] OR ("fatty"[All Fields] AND "acids"[All Fields] AND "omega 3"[All Fields]) OR "omega-3 fatty acids"[All Fields]) OR ("supplemental"[All Fields] OR "supplementating"[All Fields] OR "supplementation"[All Fields] OR "supplementation s"[All Fields] OR "supplementations"[All Fields] OR "supplemention"[All Fields]) OR ("combined modality therapy"[MeSH Terms] OR ("combined"[All Fields] AND "modality"[All Fields] AND "therapy"[All Fields]) OR "combined modality therapy"[All Fields] OR ("combination"[All Fields] AND "therapy"[All Fields]) OR "combination therapy"[All Fields]) OR (("synergist"[All Fields] OR "synergistic"[All Fields] OR "synergistical"[All Fields] OR "synergistically"[All Fields] OR "synergists"[All Fields]) AND ("effect"[All Fields] OR "effecting"[All Fields] OR "effective"[All Fields] OR "effectively"[All Fields] OR "effectiveness"[All Fields] OR "effectivenesses"[All Fields] OR "effectives"[All Fields] OR "effectivities"[All Fields] OR "effectivity"[All Fields] OR "effects"[All Fields]))) AND ("migrain"[All Fields] OR "migraine disorders"[MeSH Terms] OR ("migraine"[All Fields] AND "disorders"[All Fields]) OR "migraine disorders"[All Fields] OR "migraine"[All Fields] OR "migraines"[All Fields] OR "migraine s"[All Fields] OR "migraineous"[All Fields] OR "migrainers"[All Fields] OR "migrainous"[All Fields] OR (("episode"[All Fields] OR "episodes"[All Fields] OR "episodic"[All Fields] OR "episodically"[All Fields]) AND ("migrain"[All Fields] OR "migraine disorders"[MeSH Terms] OR ("migraine"[All Fields] AND "disorders"[All Fields]) OR "migraine disorders"[All Fields] OR "migraine"[All Fields] OR "migraines"[All Fields] OR "migraine s"[All Fields] OR "migraineous"[All Fields] OR "migrainers"[All Fields] OR "migrainous"[All Fields])) OR (("migrain"[All Fields] OR "migraine disorders"[MeSH Terms] OR ("migraine"[All Fields] AND "disorders"[All Fields]) OR "migraine disorders"[All Fields] OR "migraine"[All Fields] OR "migraines"[All Fields] OR "migraine s"[All Fields] OR "migraineous"[All Fields] OR "migrainers"[All Fields] OR "migrainous"[All Fields]) AND ("attack"[All Fields] OR "attacked"[All Fields] OR "attacker"[All Fields] OR "attacker s"[All Fields] OR "attackers"[All Fields] OR "attacking"[All Fields] OR "attacks"[All Fields])) OR (("migrain"[All Fields] OR "migraine disorders"[MeSH Terms] OR ("migraine"[All Fields] AND "disorders"[All Fields]) OR "migraine disorders"[All Fields] OR "migraine"[All Fields] OR "migraines"[All Fields] OR "migraine s"[All Fields] OR "migraineous"[All Fields] OR "migrainers"[All Fields] OR "migrainous"[All Fields]) AND ("duration"[All Fields] OR "durations"[All Fields])) OR (("migrain"[All Fields] OR "migraine disorders"[MeSH Terms] OR ("migraine"[All Fields] AND "disorders"[All Fields]) OR "migraine disorders"[All Fields] OR "migraine"[All Fields] OR "migraines"[All Fields] OR "migraine s"[All Fields] OR "migraineous"[All Fields] OR "migrainers"[All Fields] OR "migrainous"[All Fields]) AND ("pain"[MeSH Terms] OR "pain"[All Fields])))) AND (((("pain"[MeSH Terms] OR "pain"[All Fields]) AND ("reduction"[All Fields] OR "reductions"[All Fields])) OR (("headache"[MeSH Terms] OR "headache"[All Fields] OR "headaches"[All Fields] OR "headache s"[All Fields]) AND ("reduction"[All Fields] OR "reductions"[All Fields]))))	261
Embase	('curcumin'/exp OR curcumin OR 'nano-curcumin' OR 'omega-3'/exp OR 'omega-3' OR 'ω-3 fatty acids' OR 'supplementation'/exp OR supplementation OR 'combination therapy'/exp OR 'combination therapy' OR 'synergistic effects') AND ('migraine'/exp OR migraine OR 'episodic migraine'/exp OR 'episodic migraine' OR 'migraine attacks' OR 'migraine duration' OR 'migraine pain') AND ('pain reduction'/exp OR 'pain reduction' OR 'headache reduction')	144
Scopus	ALL ((Curcumin OR 'Nano-Curcumin' OR 'Omega-3' OR 'ω-3 Fatty Acids' OR Supplementation OR 'Combination therapy' OR 'Synergistic effects') AND (Migraine OR 'Episodic Migraine' OR 'Migraine attacks' OR 'Migraine duration' OR 'Migraine pain') AND ('pain reduction' OR 'Headache reduction'))	660
Web of Science	(Curcumin OR 'Nano-Curcumin' OR 'Omega-3' OR 'ω-3 Fatty Acids' OR Supplementation OR 'Combination therapy' OR 'Synergistic effects') AND (Migraine OR 'Episodic Migraine' OR 'Migraine attacks' OR 'Migraine duration' OR 'Migraine pain') AND ('pain reduction' OR 'Headache reduction') (All Fields)	176
Cochrane Library	(Curcumin OR 'Nano-Curcumin' OR 'Omega-3' OR 'ω-3 Fatty Acids' OR Supplementation OR 'Combination therapy' OR 'Synergistic effects') AND (Migraine OR 'Episodic Migraine' OR 'Migraine attacks' OR 'Migraine duration' OR 'Migraine pain') AND ('pain reduction' OR 'Headache reduction') in All Text	391

Total = 1,632. Original searches ended in October 2025. Database counts are restored from the original submitted search breakdown.

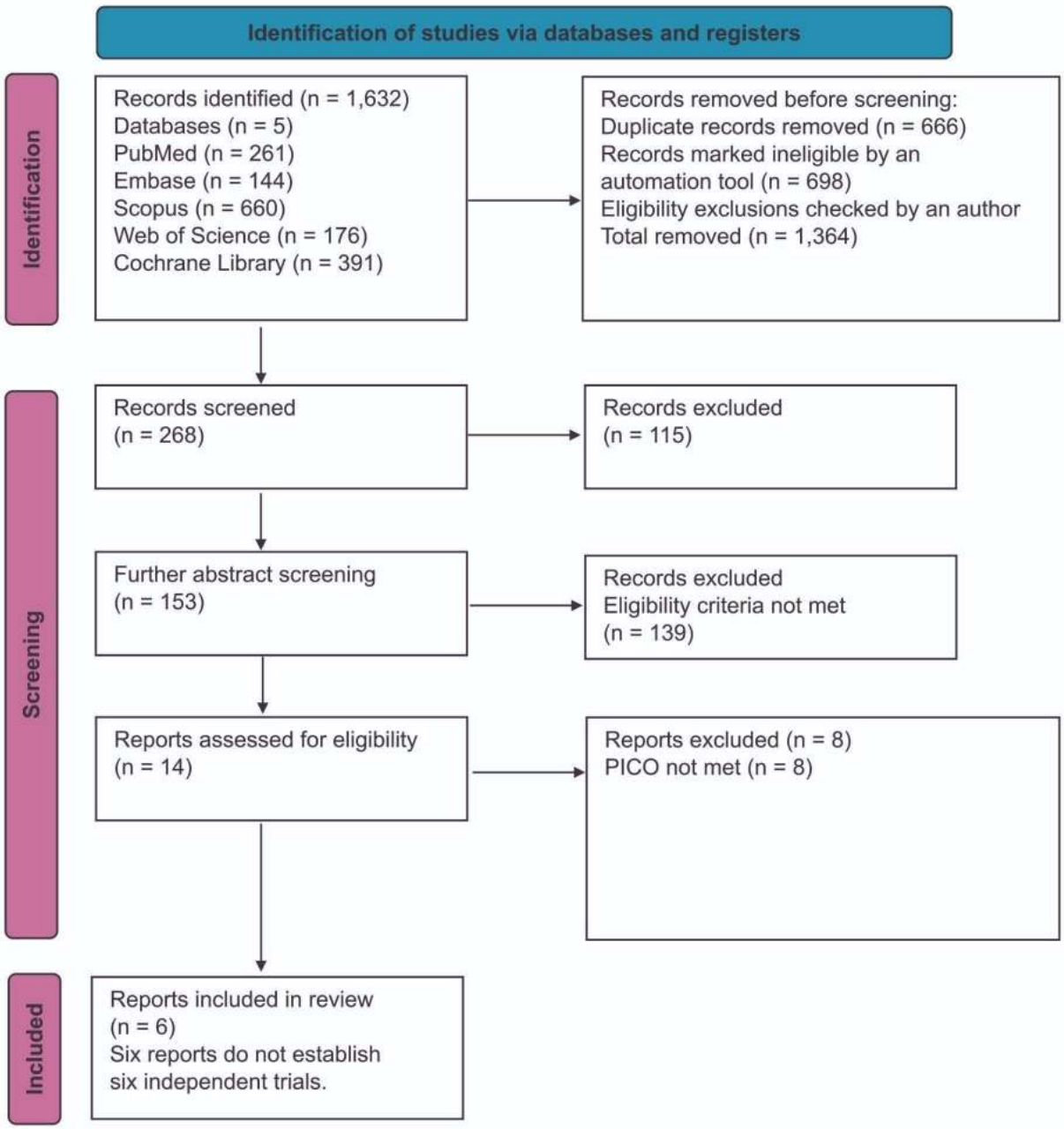

Figure 1. Study selection for the five-database search through October 2025. Of 1,632 identified records, 1,364 were removed before screening: 666 duplicates and 698 records marked ineligible by an automation tool and checked by an author against the eligibility criteria. The remaining 268 records were screened. Initial screening excluded 115 records; further abstract screening excluded 139 of the remaining 153 records. Fourteen reports underwent full-text eligibility assessment; eight did not meet the PICO criteria, leaving six included reports. Six reports do not establish six independent trials.

and 95% confidence intervals were reconstructed from the reported endpoint means, standard errors and arm sizes using independent-group Welch t intervals (Supplementary Table S2). These intervals are not baseline-adjusted, intention-to-treat estimates or multiplicity-adjusted pairwise tests. They are presented separately from the source ANCOVA and ANOVA P values. This departs from the registered plan for meta-analysis: repeated reporting cannot supply independent effect estimates and overlap in the remaining reports is unresolved. I^2 and heterogeneity tests were therefore not calculated. Funnel plots and small-study-effect tests were not performed because a sufficient set of independent quantitative trials was unavailable.

Risk of bias assessment

RoB 2 judgments addressed assignment to combination supplementation versus placebo at two months. Outcome-specific judgments considered randomization, deviations from intended interventions, missing outcome data, outcome measurement and selection of the reported result. JK independently reassessed the judgments during revision. Clinical assessments were supplemented by ancillary assessments of reported biomarker outcomes to display the available information for all retained publications; these do not expand the clinical synthesis. Table 5 maps report rows to the specified outcomes. Multiple domains with some concerns were considered jointly when determining overall risk. Detailed signaling responses and the limitations of available source reporting appear in Supplementary section S4.

Results

Study selection

The search identified 1,632 records: 261 from PubMed, 144 from Embase, 660 from Scopus, 176 from Web of Science and 391 from the Cochrane Library. A total of 1,364 records were removed before screening: 666 duplicate records and 698 records marked ineligible by an automation tool. An author checked the 698 records against the eligibility criteria and confirmed their exclusion. The remaining 268 records underwent title and abstract screening. Of these, 115 records were excluded at the initial screening stage, leaving 153 records for further relevance screening. A further 139 records were excluded because they did not meet the eligibility criteria. Fourteen reports underwent full-text eligibility assessments; eight did not meet the PICO criteria, leaving six reports included in the review (Figure 1). These six reports must not be interpreted as six independent trials. The original record-level search exports were unavailable, limiting independent verification of deduplication and the complete study-selection audit trail.

Characteristics of retained reports

Six reports originated from the same Iranian research group and described four-arm randomized comparisons over two months (10–15). Reported sample sizes were 72–80, with predominantly female participants. Eligibility generally covered ages 20–50 years. Table 2 summarizes participant characteristics and funding; the table note identifies publications reporting the same trial. Supplementary Table S1 distinguishes verified common registration from probable or unresolved linkage; six reports must not be interpreted as six independent trials.

Interventions and comparators

Participants continued standard prophylaxis, including tricyclic antidepressants (25–50 mg/day) and propranolol (20–40 mg/day). The four arms were omega-3 plus nano-curcumin, omega-3 with matched nano-curcumin placebo, nano-curcumin with matched omega-3 placebo, and both placebos. Supplements were oral and treatment lasted two months. The described regimen comprised two 1,250-mg fish-oil capsules daily, providing 1,200 mg EPA plus 600 mg DHA, and 80 mg/day nano-curcumin. The 1,800-mg EPA-plus-DHA amount should not be interpreted as a lower dose than 2,500 mg of fish-oil capsule material. Matching placebos contained paraffin oil (Table 3).

Clinical outcomes

At two months, mean attack frequency was 0.62, 1.67, 1.82 and 2.22 attacks/week for combination therapy, omega-3, nano-curcumin and placebo, respectively. The calculated unadjusted endpoint differences for combination therapy were −1.05 versus omega-3, −1.20 versus nano-curcumin and −1.60 versus placebo attacks/week. The adjusted overall four-group comparison was significant (P=0.009). The 2019 report describes significant post-hoc frequency comparisons against placebo and nano-curcumin without exact pairwise P values; the 2017 report additionally gives P = 0.01 versus omega-3 and P<0.001 versus nano-curcumin (13,14). The exploratory unadjusted combination-versus-placebo difference was -1.60 (95% CI -2.41 to -0.79) attacks/week; the intervals for all three comparators are shown in Supplementary Table S2. For severity, the calculated endpoint differences were −0.40 versus omega-3, −0.84 versus nano-curcumin, and −1.76 versus placebo on the source's 1–10 scale. Although the four-group comparison was significant (P=0.02), the 2019 report states

Table 2. Characteristics of retained reports

Report	Participants reported	Sex	Migraine eligibility information	Funding
Soveyd et al.(11)	72	Male: 20% female: 80%	<15 days/ month, >3 migraine attacks/month (≥1 attack/week)	N/R
Abdolahi et al.(13)	80 enrolled; 74 analyzed	Male: 16; female: 64	<15 days/ month, >3 migraine attacks/month (≥1 attack/week)	N/R
Abdolahi et al.(14)	80 enrolled; 74 analyzed	Male: 16; female: 64	<15 days per month, > 3 migraine attacks per month or ≥ 1 attack per week	None
Honarvar et al.(12)	80	Male: 16; female: 64	<15 days/month, >3 migraine attacks/month (≥1 attack/week)	None
Abdolahi et al.(10)	80 enrolled; 74 analyzed	Male: 16; female: 64	Episodic migraine stated; headache-day threshold internally inconsistent	None
Abdolahi et al.(15) Companion report	80 enrolled; 74 completers	Male: 16; female: 64	Not specified in extracted eligibility information	Not explicitly reported

All six reports originated in Iran and describe a randomized four-arm trial or a companion report, adults aged 20–50 years, and two-month supplementation. Episodic migraine is the reported diagnosis; the 2021 headache-day threshold is internally inconsistent. The combination is omega-3 plus nano-curcumin; comparators are omega-3 alone, nano-curcumin alone, and placebo. Counts are report-level and must not be summed. The 2018, 2019 and 2021 Abdolahi reports share NCT02532023; overlap with 2017 is probable, and linkage of Soveyd/Honarvar is unresolved (Supplementary Table S1). N/R = not reported; M/F = male/female. Sex counts may refer to enrolled participants rather than completers.

that combination therapy did not differ significantly from either monotherapy; it did not report an exact pairwise severity P value versus placebo. Duration decreased within the combination arm (P=0.005), but the overall between-group tests were not significant (endpoint P=0.64; change P=0.26). The source did not report confidence intervals for these comparisons. Exploratory unadjusted severity and duration intervals are supplied in Supplementary Table S2 and do not replace the source adjusted analyses. Soveyd et al.(11) and Honarvar et al.(12) also reported reductions in attack frequency. The available indexed reports did not provide sufficient arm-specific follow-up data to extract an additional between-group treatment estimate; these findings were retained qualitatively.

Six withdrawals associated with changes in treatment or medication were reported (10,13,14). These were not classified as confirmed supplement-related adverse events. The short follow-up and limited adverse-event reporting do not establish long-term safety (Table 4).

Risk of bias

Risk of bias was assessed using RoB 2 (16), supported by source publications, published protocol, and registry (17,18). The three quantitatively extracted clinical outcomes and the ancillary biomarker outcomes had some concerns overall. Table 5 and Figure 2 present the specified outcome profiles for all six reports. Supplementary Figure S1 summarizes these report profiles descriptively. All three clinical outcomes had some concerns for randomization, missing outcome data, and selection of the reported result, and low risk of deviation from intended interventions and outcome measurement. Randomization, coded capsules, and matched placebos support blinding, but the report did not sufficiently describe allocation concealment before enrollment. Six medication-related withdrawals left 17/20 combination and 19/20 placebo participants, without a reported missing-data sensitivity analysis. The authors assessed clinical outcomes under participant blinding. The available protocol and registry did not fully specify the exact reported analyses. These uncertainties supported some concerns overall. The public registry, first posted August 25, 2015, describes 1,000 mg/day curcumin and a planned September 2015 start, whereas outcome publications describe 80 mg/day nano-curcumin and the 2021 report describes July 2015 recruitment (17,18). The registry contains broad outcome names and internally inconsistent arm descriptions. These discrepancies limit verification of prospective agreement but do not establish actual nonadherence or selective reporting (Table 5, Figures 2 and 3).

Table 3. Intervention details by report

Report	Background prophylaxis	Daily supplements and placebos
Soveyd et al.(11)	TCA and β-blocker (propranolol)	Fish oil: 2,500 mg/day Nano-curcumin: 80 mg/day Paraffin-oil placebo
Abdolahi et al.(13)	TCA and β-blocker (propranolol)	Fish-oil capsules: 2,500 mg/day EPA + DHA: 1,800 mg/day Nano-curcumin: 80 mg/day Matched placebo capsules
Abdolahi et al.(14)	TCA and β-blocker (propranolol)	Fish-oil capsules: 2,500 mg/day EPA + DHA: 1,800 mg/day Nano-curcumin: 80 mg/day Matched placebo capsules
Honarvar et al.(12)	TCA and β-blocker (propranolol)	Fish oil: 2,500 mg/day Nano-curcumin: 80 mg/day Paraffin-oil placebo
Abdolahi et al.(10)	TCA and β-blocker (propranolol)	Fish-oil capsules: 2,500 mg/day EPA + DHA: 1,800 mg/day Nano-curcumin: 80 mg/day Matched placebo capsules
Abdolahi et al.(15) 2018 Companion report	TCA and β-blocker	Fish-oil capsules 2,500 mg/day; EPA 1,200 mg + DHA 600 mg/day; nano-curcumin 80 mg/day; matched placebos

All supplements were oral capsules. Diagnosis and eligibility details are in Table 2. All reports compare combined omega-3 plus nano-curcumin against each monotherapy and placebo. Monotherapy arms receive the placebo for the other supplement; controls receive both placebos. TCA = tricyclic antidepressant. In verified linked reports, background doses were TCA 25–50 mg/day and propranolol 20–40 mg/day. Fish-oil capsule mass (2,500 mg/day) is distinct from EPA + DHA (1,800 mg/day: 1,200 mg EPA + 600 mg DHA). Doses extracted for Soveyd and Honarvar could not be independently confirmed from their complete full texts.

Table 4. Clinical outcomes in the repeatedly reported dataset

Outcome and source	Arm	Baseline mean ± SE	Two months mean ± SE	Within-arm P	Between-group comparison
Frequency attacks/week (13, 14; repeated in 10)	Combination	2.72 ± 0.40	0.62 ± 0.08	<0.001	Four-group endpoint P = 0.009; changes P = 0.01.
	Omega-3	2.77 ± 0.26	1.67 ± 0.42	0.004	
	Nano-curcumin	2.81 ± 0.31	1.82 ± 0.27	0.009	
	Placebo	2.76 ± 0.24	2.22 ± 0.38	0.11	
Severity 1–10 scale (14; repeated in 10)	Combination	7.47 ± 0.48	5.02 ± 0.56	<0.001	Four-group endpoint P = 0.02; changes P = 0.04. No significant superiority over either monotherapy reported.
	Omega-3	7.36 ± 0.46	5.42 ± 0.52	0.001	
	Nano-curcumin	7.52 ± 0.44	5.86 ± 0.48	0.001	
	Placebo	7.39 ± 0.46	6.78 ± 0.43	0.22	
Duration hours (14; repeated in 10)	Combination	7.28 ± 1.77	4.15 ± 1.47	0.005	Four-group endpoint P = 0.64; changes P = 0.26. No significant between-group benefit.
	Omega-3	7.68 ± 1.77	5.26 ± 1.66	0.002	
	Nano-curcumin	7.44 ± 1.80	6.02 ± 1.36	0.15	
	Placebo	7.34 ± 1.43	6.68 ± 1.13	0.53	

All baseline and endpoint values are mean ± SE, not SD. Combination n=17; each comparator n=19. One clinical dataset is presented using the named arms in Abdolahi 2019 (14) . Endpoint P values are four-group ANCOVA tests; change P values are four-group ANOVA tests. Neither is a pairwise P value. Source confidence intervals were not reported. Exploratory unadjusted endpoint differences and reconstructed 95% intervals are in Supplementary Table S2. Source change rows contain rounding or typographical inconsistencies and are not reconstructed as paired treatment effects.

Table 5. Risk of bias for specified outcomes by report

Report	D1	D2	D3	D4	D5	Overall
Soveyd et al.(11) / 2018	Some concerns	Some concerns	Some concerns	Low	Some concerns	Some concerns
Abdolahi et al.(13) / 2017	Some concerns	Low	Some concerns	Low	Some concerns	Some concerns
Abdolahi et al.(14) / 2019	Some concerns	Low	Some concerns	Low	Some concerns	Some concerns
Honarvar et al.(12) / 2021	Some concerns	Some concerns	Some concerns	Low	Some concerns	Some concerns
Abdolahi et al.(10) / 2021	Some concerns	Low	Some concerns	Low	Some concerns	Some concerns
Abdolahi et al.(15) / 2018	Some concerns	Low	Some concerns	Low	Some concerns	Some concerns

Judgments concern the specified outcomes for assignment to combination supplementation versus placebo at two months. Outcome mapping: Soveyd—ICAM-1; Abdolahi 2017—TNF-α and attack frequency; Abdolahi 2019—COX-2/iNOS and clinical outcomes; Honarvar—IL-1β; Abdolahi 2021—VCAM and clinical outcomes; Abdolahi 2018—IL-6/hs-CRP. Biomarker assessments are ancillary to the clinical review. Rows represent report profiles, not independent trials.
D1 = randomization; D2 = deviations from intended interventions; D3 = missing outcome data; D4 = outcome measurement; D5 = selection of the reported result. "Low" means low risk. JK independently reassessed the judgments during revision. Outcome-specific signaling responses and combined-domain rationale are in Supplementary section S4. Assessments concern combination versus placebo; they do not cover every monotherapy contrast. Figure 2 matches these six rows exactly.

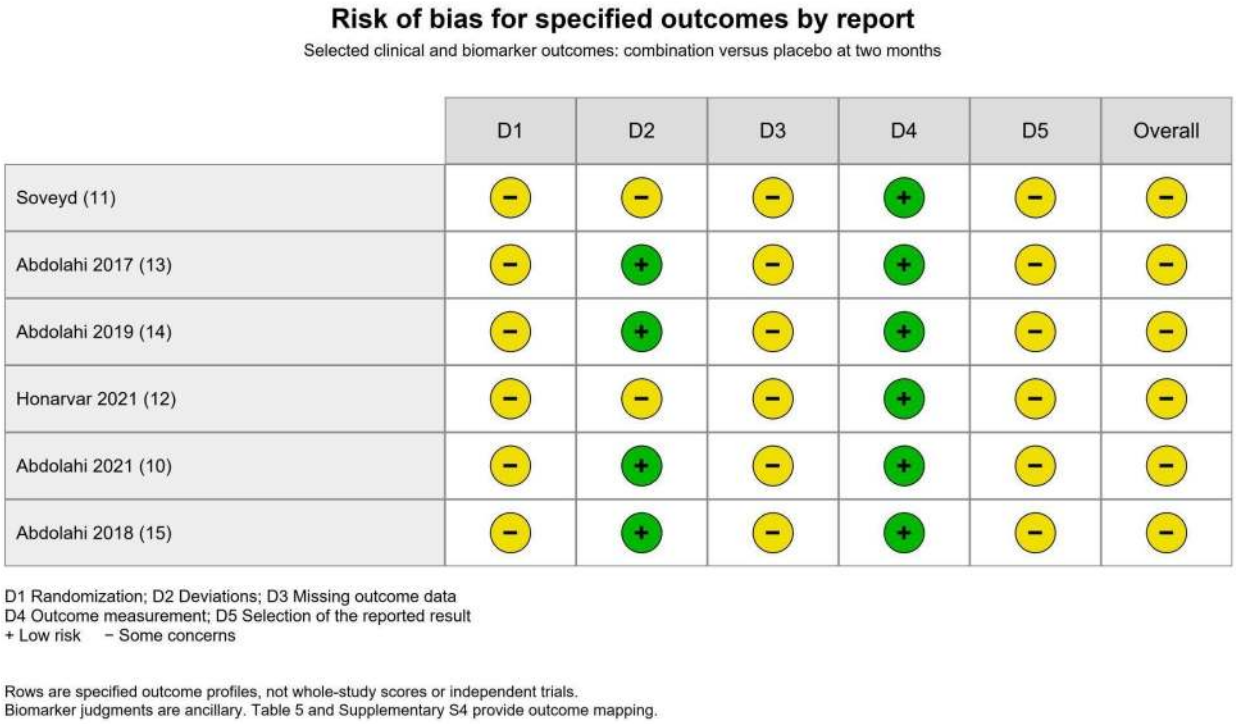

Figure 2. Risk-of-bias domain judgments for selected clinical and biomarker outcomes across six report profiles. Judgments concern assignment to combination supplementation versus placebo at two months; Table 5 maps each report to the specified outcomes. Companion publications are not independent trials. Biomarker judgments are ancillary and do not establish headache benefit.

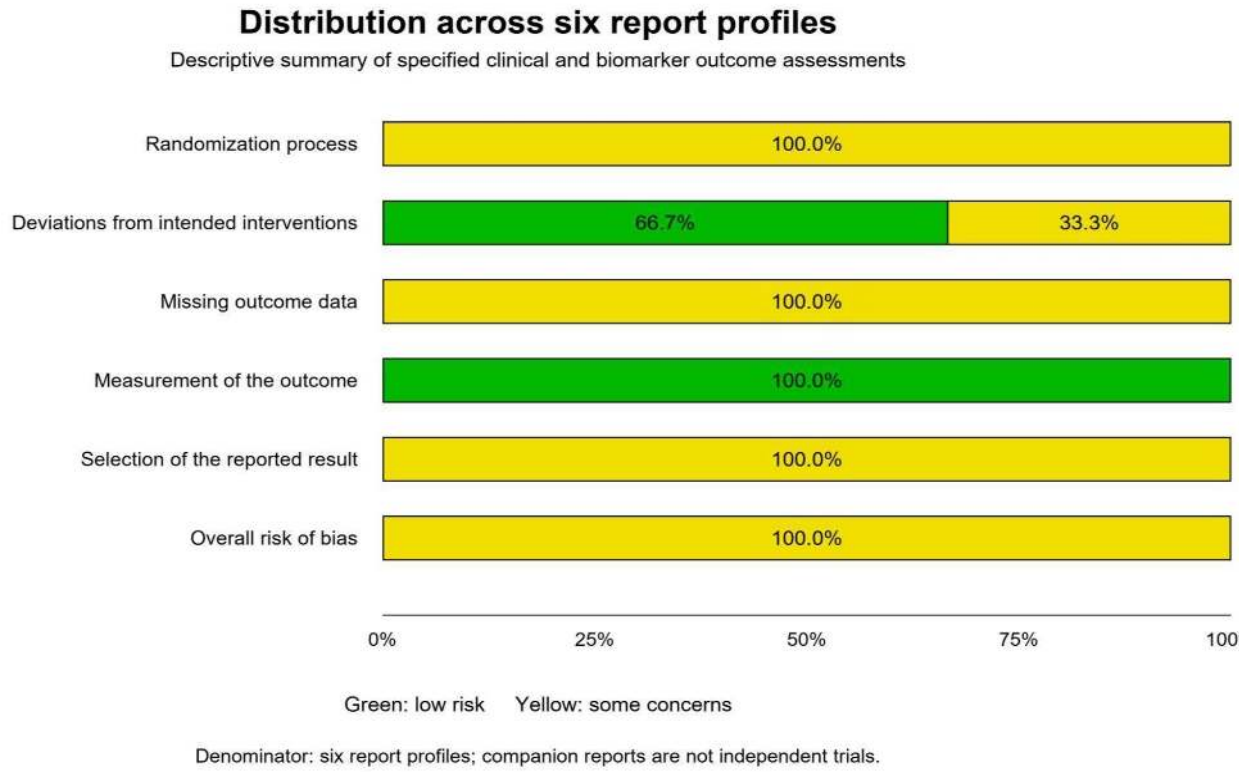

Figure 3. Distribution across six report profiles.

Discussion

This review found lower attack frequency with combination supplementation in one repeatedly reported two-month clinical dataset. Severity did not establish superiority over either monotherapy, or a within-group reduction in duration did not translate into a significant between-group benefit. The reconstructed unadjusted intervals quantify the uncertainty of raw endpoint contrasts; they do not supply the missing adjusted pairwise effects. Clinical synergy cannot be inferred without a suitable interaction analysis. The combination was studied as an adjunct to prophylaxis. It cannot be regarded as a substitute for established preventive treatment, including the CGRP-targeting options described in the American Headache Society position statement (19). Broader supplement literature provides context (20), rather than independent confirmation of this combination. Anti-inflammatory mechanisms provide biological plausibility (8,21), but ancillary biomarker changes do not establish headache benefit.

Strengths and limitations

This review distinguishes within-group changes from between-group treatment effects and evaluates frequency, severity, and duration separately. The concentration of reports within one research group in Iran and confirmed or possible participant overlap limit the independence and generalizability of the evidence. Overlap involving the Soveyd and Honarvar reports remains unresolved, so the number of unique trials and participants could not be established. The original search required pain- or headache-reduction terms, which may omit relevant publications, and ended in October 2025. Original record-level exports were unavailable for an independent deduplication audit. Further limitations include small samples, two-month follow-up, incomplete reporting of methods and adverse events, and some concerns about risk of bias across all assessed outcomes. The review team read the full Soveyd and Honarvar reports. Complete methods and outcome tables were not available for independent rechecking during this revision, limiting verification of additional arm-specific clinical data.

Ancillary biomarker assessments do not resolve missing clinical reporting. JK independently reassessed the outcome-specific judgments, but this does not overcome the primary reports' missing information. Unavailable original record-level exports limit independent verification of the selection process. The evidence does not establish durable benefits, long-term safety, optimal dosing or consistent superiority over monotherapy. Independent, adequately powered multicenter trials should prespecify clinical outcomes, comparisons against each monotherapy and placebo, missing-data analyses and adverse-event collection. Claims of synergy require a prespecified interaction analysis. Longer follow-up is needed to establish whether any benefit is sustained.

Conclusion

Combination supplementation was associated with lower migraine attack frequency in the reported two-month clinical dataset. Headache severity did not differ significantly from either monotherapy, and headache duration did not differ significantly across treatment groups. Small samples, repeated reporting of participants, and short follow-up limit the evidence. Independent, adequately powered trials are needed to determine comparative efficacy and long-term safety.

References

1. Chen HH, Heath KM, Patel PR. Migraine. Phys Med Rehabil Clin N Am 2025;36:701–14. Doi:10.1016/j.pmr.2025.08.002.
2. Dorsey S, Ijaz A, Ahmed F. Migraine: symptoms, types, pathophysiology and diagnosis. BJA Educ 2025;25:439–45. Doi:10.1016/j.bjae.2025.07.004.
3. Eigenbrodt AK, Ashina H, Khan S, Diener H-C, Mitsikostas DD, Sinclair AJ, et al. Diagnosis and management of migraine in ten steps. Nat Rev Neurol 2021;17:501–14. Doi:10.1038/s41582-021-00509-5.
4. Kursun O, Yemisci M, van den Maagdenberg AMJM, Karatas H. Migraine and neuroinflammation: the inflammasome perspective. J Headache Pain 2021;22. Doi:10.1186/s10194-021-01271-1.
5. Saha S, Chowdhury D, Wadhwa M, Sarkar R, Raval D, Patel I, et al. Impact of migraine on productivity and efficiency among adult population in India: a scoping review. J Headache Pain 2025;26. Doi:10.1186/s10194-025-02112-1.
6. Wijeratne T, Martelletti P. Ergotamine, triptans, and the global challenge of medication-overuse headache: a call to action from Asia–Oceania. J Headache Pain 2025;26. Doi:10.1186/s10194-025-02172-3.
7. Medoro A, Davinelli S, Colletti A, Di Micoli V, Grandi E, Fogacci F, et al. Nutraceuticals as Modulators of Immune Function: A Review of Potential Therapeutic Effects. Prev Nutr Food Sci 2023;28:89–107. Doi:10.3746/pnf.2023.28.2.89.
8. Bodur M, Yilmaz B, Ağagündüz D, Ozogul Y. Immunomodulatory Effects of Omega-3 Fatty Acids: Mechanistic Insights and Health Implications. Mol Nutr Food Res 2025;69. Doi:10.1002/mnfr.202400752.
9. Peng Y, Ao M, Dong B, Jiang Y, Yu L, Chen Z, et al. Anti-Inflammatory Effects of Curcumin in the Inflammatory Diseases: Status, Limitations and Countermeasures. Drug Des Devel Ther 2021;Volume 15:4503–25. Doi:10.2147/DDDT.S327378.
10. Abdolahi M, Karimi E, Sarraf P, Tafakhori A, Siri G, Salehinia F, et al. The omega-3 and Nano-curcumin effects on vascular cell adhesion molecule (VCAM) in episodic migraine patients: a randomized clinical trial. BMC Res Notes 2021;14. Doi:10.1186/s13104-021-05700-x.
11. Soveyd N, Abdolahi M, Djalali M, Hatami M, Tafakhori A, Sarraf P, et al. The Combined Effects of ω -3 Fatty Acids and Nano-Curcumin Supplementation on Intercellular Adhesion Molecule-1 (ICAM-1) Gene Expression and Serum Levels in Migraine Patients. CNS Neurol Disord Drug Targets 2018;16:1120–6. Doi :10.2174/1871527317666171213154749.
12. Honarvar NM, Soveid N, Abdolahi M, Djalali M, Hatami M, Karzar NH. Anti-Neuroinflammatory Properties of n-3 Fatty Acids and Nano- Curcumin on Migraine Patients from Cellular to Clinical Insight: A Randomized, Double-Blind and Placebo-Controlled Trial. Endocr Metab Immune Disord Drug Targets 2021;21:365–73. Doi:10.2174/1871530320666200729144430.
13. Abdolahi M, Tafakhori A, Togha M, Okhovat AA, Siassi F, Eshraghian MR, et al. The synergistic effects of -3 fatty acids and nano-curcumin supplementation on tumor necrosis factor (TNF)-α gene expression and serum level in migraine patients. Immunogenetics 2017;69:371–8. Doi:10.1007/s00251-017-0992-8.
14. Abdolahi M, Jafarieh A, Sarraf P, Sedighiyan M, Yousefi A, Tafakhori A, et al. The Neuromodulatory Effects of ω-3 Fatty Acids and Nano-Curcumin on the COX-2/ iNOS Network in Migraines: A Clinical Trial Study from Gene Expression to Clinical Symptoms. Endocr Metab Immune Disord Drug Targets 2019;19:874–84. Doi:10.2174/1871530319666190212170140.
15. Abdolahi M, Sarraf P, Javanbakht MH, Honarvar NM, Hatami M, Soveyd N, et al. A Novel Combination of ω-3 Fatty Acids and Nano-Curcumin Modulates Interleukin-6 Gene Expression and High Sensitivity C-reactive Protein Serum Levels in Patients with Migraine: A Randomized Clinical Trial Study. CNS Neurol Disord Drug Targets 2018;17:430–8. Doi:10.2174/1871527317666180625101643.
16. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 2019. Doi:10.1136/bmj.l4898.
17. Abdolahi M, Honarvar NM, Tafakhori A, Sarraf P, Hatami M, Soveyd N, et al. The Combined Effects of Omega3 Fatty Acids and Nano Curcumin Supplementation on Gene Expression and Serum Levels of Some Inflammatory and Endothelial Factors in Migraine Patients: Studyprotocol for a Randomized Controlled Trial. Int J Pharm Sci Invent 2016;5:12–7.

18. Tehran University of Medical Sciences. NCT02532023: The combined effects of omega3 fatty acids and curcumin supplementation on inflammatory and endothelial factors in migraine patients. ClinicalTrials.gov. First posted August 25, 2015. https://clinicaltrials.gov/study/NCT02532023 Accessed October 5, 2026.
19. Charles AC, Digre KB, Goadsby PJ, Robbins MS, Hershey A. Calcitonin gene-related peptide-targeting therapies are a first-line option for the prevention of migraine: An American Headache Society position statement update. Headache: The Journal of Head and Face Pain 2024;64:333–41. Doi:10.1111/head.14692.
20. Talandashti MK, Shahinfar H, Delgarm P, Jazayeri S. Effects of selected dietary supplements on migraine prophylaxis: A systematic review and dose–response meta-analysis of randomized controlled trials. Neurological Sciences 2025;46:651–70. Doi:10.1007/s10072-024-07794-0.
21. Mohseni M, Sahebkar A, Askari G, Johnston TP, Alikiaii B, Bagherniya M. The clinical use of curcumin on neurological disorders: An updated systematic review of clinical trials. Phytotherapy Research 2021;35:6862–82. Doi:10.1002/ptr.7273.

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Authors' contribution: All authors contributed to the conceptualization, analysis, writing, revising, editing, and final submission of the manuscript.
Conflict of interest: The authors declare no conflict of interest related to the preparation and content of this work.
Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.
Human and animal rights: All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).
Availability of data: All results are included in the study, and it was registered with PROSPERO.
Use of AI tools: The authors acknowledge the use of AI tools in this work. Grammarly and Copilot (GPT-5) by Microsoft were used solely for minor language corrections and readability improvements, and all revisions were carefully reviewed and verified by the authors. No content was generated by these or any other AI services.