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Supplementary

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

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Supplement 1. Report to trial linkage

Six publications are report units, not six independent trials. The linkage below prevents double counting without assuming that unresolved reports constitute new cohorts.

Table S1. Report-to-trial linkage

Report	Linkage classification	Supporting information and limitation
Abdolahi et al.(15) 2018	Verified common registration	NCT02532023; four arms; 80 enrolled and 74 completers. Provides methods and biomarker outcomes.
Abdolahi et al.(14) 2019	Verified common registration	NCT02532023; same four-arm design, 17/19/19/19 analyzed; clinical baseline and outcome values.
Abdolahi et al.(10) 2021	Verified common registration	NCT02532023; repeated clinical values and same analyzed arm sizes.
Abdolahi et al.(13) 2017	Probable overlap	Matching clinical data, investigators and intervention support overlap; independently verified registration linkage remains unavailable.
Soveyd et al.(11) 2018	Unresolved	72 participants reported; common investigators and regimen are suggestive, but full-text cohort identity and outcome-specific denominators remain unverified.
Honarvar et al.(12) 2021	Unresolved	80 participants reported; common investigators and regimen are suggestive, but complete full-text cohort identity remains unverified.

The 2018, 2019 and 2021 reports describe one registered trial. Probable and unresolved linkage must not be treated as proof of independence. The total number of unique participants across all reports cannot be established. Clinical values reproduced across linked publications are extracted once.

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Supplement 2. Exploratory unadjusted clinical contrasts

Table S2. Combination minus comparator at two months

Outcome	Comparator	Mean difference	95% CI
Frequency (attacks/week)	Omega-3	-1.05	-1.94 to -0.16
Frequency (attacks/week)	Nano-curcumin	-1.20	-1.79 to -0.61
Frequency (attacks/week)	Placebo	-1.60	-2.41 to -0.79
Severity (1–10 scale)	Omega-3	-0.40	-1.95 to 1.15
Severity (1–10 scale)	Nano-curcumin	-0.84	-2.34 to 0.66
Severity (1–10 scale)	Placebo	-1.76	-3.20 to -0.32
Duration (hours)	Omega-3	-1.11	-5.62 to 3.40
Duration (hours)	Nano-curcumin	-1.87	-5.94 to 2.20
Duration (hours)	Placebo	-2.53	-6.31 to 1.25

Derived from endpoint means ± SE and n=17 for combination, n=19 per comparator in Table 4 of Abdolahi 2019 (14). For independent groups: SE difference = $\sqrt{(SE_{combination}^2 + SE_{comparator}^2)}$; Welch degrees of freedom = $(a+b)^2/[a^2/(17-1)+b^2/(19-1)]$, where a and b are the respective squared standard errors. The interval is difference ± $t_{0.975,df}$ × SE difference. Negative values favor combination for these outcomes. Calculations use rounded published values. No baseline adjustment, missing-data imputation or multiplicity correction is applied. These exploratory intervals are not the paper's ANCOVA contrasts and must not be cited as adjusted efficacy tests. Source paired-change rows were not used, and change-score intervals were not inferred without valid paired variances.

Supplement 3. Search documentation

Original five database search

The following strategies and counts document the original five-database search through October 2025. Exact execution dates and record-level exports were unavailable during revision. These historical searches were not re-executed.

PubMed — reported records 261

("curcumin"[Supplementary Concept] OR "curcumin"[All Fields] OR "curcumin"[MeSH Terms] OR "curcumin s"[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])))

Embase — reported records 144

('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')

Scopus — reported records 660

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'))

Web of Science — reported records 176

(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)

Cochrane — reported records 391

(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

Supplement 4. Outcome specific risk of bias record

Scope: effect of assignment to combination supplementation versus placebo at two months. JK independently reassessed the judgments during revision, as confirmed by the authors. Judgments describe risk of bias, not trial eligibility or proof of misconduct.

Source availability

Source availability: author-deposited 2018 IL-6/hs-CRP and 2019 COX-2/iNOS full texts, the published 2021 VCAM article and public ClinicalTrials.gov record were checked during revision. The supplied assessment record also cites the published protocol and earlier extracted 2017 information. The review team screened and read the full texts of all included reports, including Soveyd and Honarvar. Independent source rechecking during this revision used indexed primary abstracts and existing extraction for these two reports because their complete methods and outcome tables were not available in the revision materials. No author contact was undertaken. Missing information is retained in signaling responses.

Selected results

1. Headache attack frequency: profile A. Combination versus placebo, two-month endpoint/assay result; no duplicate count of the same outcome from linked publications. Overall: some concerns.

2. Headache severity: profile A. Combination versus placebo, two-month endpoint/assay result; no duplicate count of the same outcome from linked publications. Overall: some concerns.

3. Headache duration: profile A. Combination versus placebo, two-month endpoint/assay result; no duplicate count of the same outcome from linked publications. Overall: some concerns.

4. TNF- serum: profile B. Combination versus placebo, two-month endpoint/assay result; no duplicate count of the same outcome from linked publications. Overall: some concerns.

5. TNF- gene expression: profile B. Combination versus placebo, two-month endpoint/assay result; no duplicate count of the same outcome from linked publications. Overall: some concerns.

6. COX-2 serum: profile A. Combination versus placebo, two-month endpoint/assay result; no duplicate count of the same outcome from linked publications. Overall: some concerns.

7. COX-2 gene expression: profile A. Combination versus placebo, two-month endpoint/assay result; no duplicate count of the same outcome from linked publications. Overall: some concerns.

8. iNOS serum: profile A. Combination versus placebo, two-month endpoint/assay result; no duplicate count of the same outcome from linked publications. Overall: some concerns.

9. iNOS gene expression: profile A. Combination versus placebo, two-month endpoint/assay result; no duplicate count of the same outcome from linked publications. Overall: some concerns.

10. VCAM serum: profile A. Combination versus placebo, two-month endpoint/assay result; no duplicate count of the same outcome from linked publications. Overall: some concerns.

11. VCAM gene expression: profile A. Combination versus placebo, two-month endpoint/assay result; no duplicate count of the same outcome from linked publications. Overall: some concerns.

12. IL-6 serum: profile A. Combination versus placebo, two-month endpoint/assay result; no duplicate count of the same outcome from linked publications. Overall: some concerns.

13. IL-6 gene expression: profile A. Combination versus placebo, two-month endpoint/assay result; no duplicate count of the same outcome from linked publications. Overall: some concerns.

14. hs-CRP serum: profile A. Combination versus placebo, two-month endpoint/assay result; no duplicate count of the same outcome from linked publications. Overall: some concerns.

15. ICAM-1 serum: profile C. Combination versus placebo, two-month endpoint/assay result; no duplicate count of the same outcome from linked publications. Overall: some concerns.

16. ICAM-1 gene expression: profile C. Combination versus placebo, two-month endpoint/assay result; no duplicate count of the same outcome from linked publications. Overall: some concerns.

17. IL-1β serum: profile C. Combination versus placebo, two-month endpoint/assay result; no duplicate count of the same outcome from linked publications. Overall: some concerns.

18. IL-1β gene expression: profile C. Combination versus placebo, two-month endpoint/assay result; no duplicate count of the same outcome from linked publications. Overall: some concerns.

Signaling responses and reasons

Y = yes; PY = probably yes; PN = probably no; N = no; NI = no information; NA = not applicable. Conditional questions not reached by the preceding responses are NA. Profiles are applied separately to each listed outcome, not as blanket publication scores.

Profile A

D1 — 1.1 Y; 1.2 NI; 1.3 PN. Some concerns. Permuted-block or stratified randomization is described. A third person coded capsules, and external personnel allocated/enrolled participants, but a pre-enrollment concealment mechanism cannot be established. No convincing baseline pattern suggests failed randomization; nonsignificant P values alone are not the basis for this decision.

D2 — 2.1 PN; 2.2 PN; 2.3–2.5 NA; 2.6 PY; 2.7 NA. Low risk. Participants and care providers were probably blinded by matching capsules. Available cases appear analyzed in allocated arms; exclusion for missing outcomes is handled under D3, not counted again as deviation bias. No evidence of trial-context departures was identified. The registry dose discrepancy is not evidence of differential adherence after randomization.

D3 — 3.1 N; 3.2 N; 3.3 PY; 3.4 PN. Some concerns. Combination 17/20 and placebo 19/20 analyzed, with medication changes accounting for losses. Such changes could relate to headache or inflammatory state, but their reasons do not establish that missingness probably depended on the actual outcome. No sensitivity analysis demonstrates robustness. The unequal small numbers were considered; they are not alone proof of outcome-dependent loss.

D4 — Clinical: 4.1 PN; 4.2 PN; 4.3 PN; 4.4–4.5 NA. Laboratory: 4.1 PN; 4.2 PN; 4.3 NI; 4.4 PN; 4.5 NA. Low risk. Clinical outcomes were assessed with blinded participants; subjective assessment alone does not imply bias. Laboratory assays were objective and applied comparably. Even where assessor masking was not explicit, knowledge of allocation was judged unlikely to materially change standardized assay measurements. The flow-diagram and monotherapy-label inconsistencies remain extraction/reporting cautions.

D5 — 5.1 NI; 5.2 PN; 5.3 NI. Some concerns. Registry names clinical and laboratory outcomes at two months. The protocol specifies broad tests, including ANCOVA, but not the complete result-specific model, covariates, multiplicity or missing-data strategy before unblinding. Protocol publication and recruitment dates do not establish prospective analysis locking. No direct evidence of selection between multiple measurements was identified; selective choice among analyses cannot be ruled out.

Overall: some concerns. Several domains contain uncertainty; they were considered jointly. Available evidence does not show bias in a single domain or a combination sufficiently serious to support high risk. Low risk is not supported. Unknown bias direction is not inferred to favor a particular arm.

Profile B

Probable 2017 linkage: shared clinical and baseline data support borrowing trial-conduct evidence, with uncertainty explicitly retained. Apply the profile A responses to the TNF-α results. The linked

protocol lists TNF-α, but applicability is not certain; D5 remains some concerns, with 5.1 NI, 5.2 NI, 5.3 NI.

Overall: some concerns. Several domains contain uncertainty; they were considered jointly. Available evidence does not show bias in a single domain or a combination sufficiently serious to support high risk. Low risk is not supported. Unknown bias direction is not inferred to favor a particular arm.

Profile C

For the ICAM-1 and IL-1β results, linkage to the registry trial has not been established and detailed current full texts were unavailable. Do not borrow the 74-completer denominator or concealment assurances from other reports.

D1 — 1.1 NI; 1.2 NI; 1.3 NI. Some concerns. Randomized design is reported/indexed, but sequence, concealment and complete baseline evidence are unavailable.

D2 — ICAM-1: 2.1 NI; 2.2 NI; 2.3 NI; 2.4–2.5 NA; 2.6 NI; 2.7 NI. IL-1β: 2.1 PN; 2.2 PN; 2.3–2.5 NA; 2.6 NI; 2.7 NI. Some concerns. Honarvar describes double blinding; allocation-preserving analysis is not verifiable for either publication. Missing information does not establish actual harmful deviations.

D3 — 3.1 NI; 3.2 N; 3.3 NI; 3.4 NI. Some concerns. Outcome-specific randomized and analyzed denominators, reasons for loss and sensitivity analyses cannot be verified from available information.

D4 — 4.1 PN; 4.2 PN; 4.3 NI; 4.4 PN; 4.5 NA. Low risk. Primary abstracts specify objective ELISA and real-time PCR methods. There is no evidence of differential measurement, and allocation knowledge is unlikely to materially influence these assay outcomes.

D5 — 5.1 NI; 5.2 NI; 5.3 NI. Some concerns. No verified report-specific prespecified analysis plan or secure protocol linkage. No evidence sufficient to conclude that selective reporting actually occurred.

Overall: some concerns. Several domains contain uncertainty; they were considered jointly. Available evidence does not show bias in a single domain or a combination sufficiently serious to support high risk. Low risk is not supported. Unknown bias direction is not inferred to favor a particular arm.

Protocol and registration discrepancies

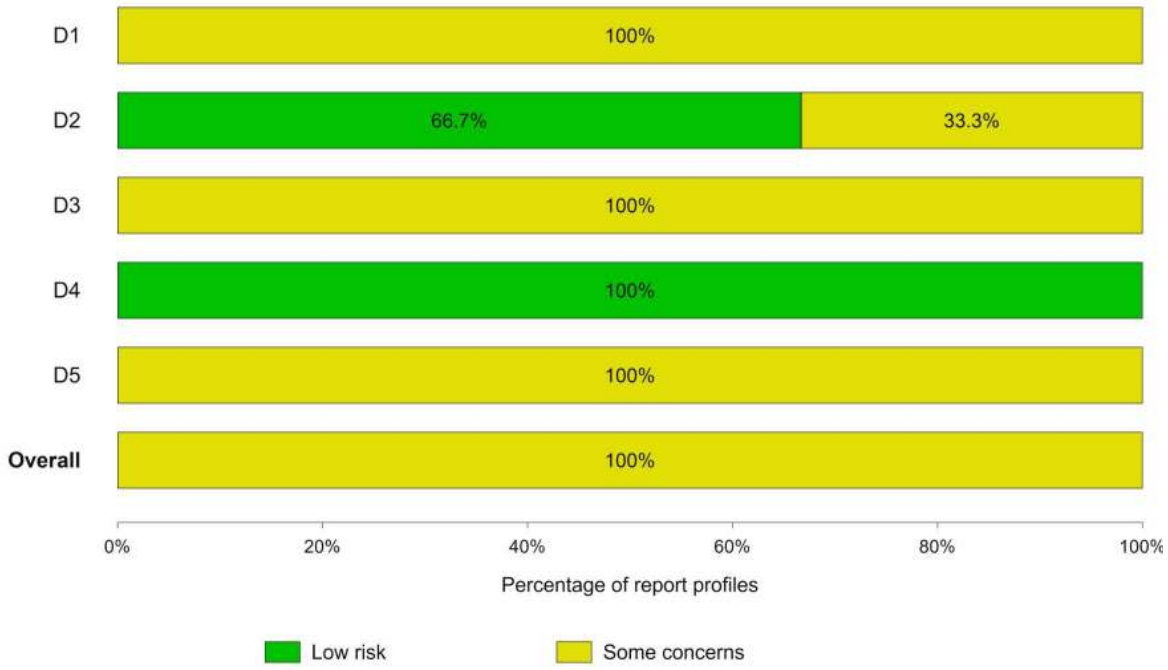
The registry record describes 1,000 mg/day curcumin, whereas the published protocol and outcome reports describe 80 mg/day nano-curcumin. The registry's planned September 2015 start date also differs from the July 2015 recruitment description in the 2021 report. These discrepancies are reported transparently and prevent assuming fully prospective agreement; they do not by themselves prove treatment deviations or selective reporting. The protocol was used as supporting documentation, not added as another included results report .

Supporting sources

1. 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.
2. 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
3. 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.
4. 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.
5. Higgins JP, Savović J, Page. Matthew J, Sterne JA, et al. Revised Cochrane risk-of-bias tool for randomized trials (RoB 2). Cochrane Methods 2019. https://www.cochrane.de/sites/cochrane.de/files/uploads/RoB_2.0_guidance_2019.pdf

Supplementary Figure S1

Risk of bias summary (RoB 2)



Note: Six report profiles, not independent trials (n = 6).

Figure S1. Distribution of risk-of-bias judgments across six report profiles. D1, D3, D5 and overall: 100% some concerns; D2: 66.7% low risk and 33.3% some concerns; D4: 100% low risk. Denominator = six report profiles, not independent trials or all possible clinical contrasts. Table 5 and S4 specify the selected clinical and biomarker outcomes. This distribution is descriptive and must not be interpreted as evidence weighting or a quality score.