*Original Article*

# Effect of omega-3 fatty acids on sleep: a systematic review and meta-analysis of randomized controlled trials

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**Omega-3 long-chain polyunsaturated fatty acids (LC-PUFAs) have been reported to improve sleep quality in several studies, but meta-analyses have been inconclusive. We conducted this study to investigate the effects of omega-3 LC-PUFAs on sleep in clinical trials. The study was planned in accordance with the criteria of the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-2020), and was performed by searching PubMed, The Cochrane Library, and Ichushi-web databases. Randomized controlled trials and clinical trials with control groups were included. Finally, eight studies were selected for inclusion in this study. Sleep efficiency was significantly higher in the omega-3 LC-PUFA group than in the control group, while sleep latency and total sleep duration did not differ significantly. Subjectively assessed sleep was significantly improved by omega-3 LC-PUFA, but heterogeneity was so high that a subgroup analysis based on dose of omega-3 supplementation was performed. It showed low heterogeneity and significant improvement in the omega-3 LC-PUFA group compared with the control group. Omega-3 LC-PUFAs have been shown to may improve sleep quality. Further studies are needed to confirm the relationship between omega-3 LC-PUFAs and sleep. The protocol for this review was registered in UMIN000052527.**

***Key Words*: omega-3, sleep, meta-analysis**

It has recently been reported that poor sleep quality is closely associated with the progression of lifestyle-related diseases such as diabetes, hypertension, ischemic heart disease, and depression.[1–6] Thus, choosing an effective strategy to improve sleep quality is one of the most important issues for maintaining good health.

With the increase in sleep research worldwide, sleep problems have been increasingly recognized as an important issue and are being included in the national health strategies in many countries, including the United States and Japan.[7,8] In the United States, "Sleep Health" has been identified as an important factor in the "Healthy People 2020" policy, with specific goals and measures to promote sleep health.[7]

Many reports have been published on the relationship between sleep and nutrients, which has become an increasing focus among the general public.[9–11] Among the various nutrients, the role of omega-3 long-chain polyunsaturated fatty acids (LC-PUFAs) in sleep has been increasingly studied.[12] Various lines of evidence have indicated that omega-3 LC-PUFAs contribute to sleep health. Omega-3 LC-PUFAs are unsaturated fatty acids present in the human body, but cannot be synthesized there. Omega-3 LC-PUFAs include docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), and α-linolenic acid, which are found in fish. Omega-3 LC-PUFAs have been reported to exert pharmacological effects such as lowering blood lipid levels, reducing the risk of developing cardiovascular disease, and improving brain function.[13–23] The relationship between omega-3 supplementation and sleep quality has been proven previously. For example, Del Brutto *et al.*[24] reported in one epidemiological study that adults with good sleep quality had a higher intake of oily fish. In addition, Katagiri *et al.*[25] reported that poor sleep quality was associated with low fish intake. Since then, several human intervention trials have been conducted on infants by Judge *et al.*,[26] on children by Montgomery *et al.*,[27] and on healthy adults by Patan *et al.*[28] and Yokoi-Shimizu *et al.*,[29] with positive results in terms of sleep efficiency, onset latency, sleep duration, and subjectively assessed sleep. In 2021, Dai *et al.*[12] conducted a meta-analysis of omega-3 LC-PUFAs and sleep, but the results did not reveal a significant relationship between them. As mentioned above, the importance of improving sleep quality has further increased in recent years, and several new studies on sleep have been reported since the report on the meta-analysis by Dai *et al.*[12] Therefore, we hypothesized that omega-3 LC-PUFAs may also have an effect on sleep in humans, and the objective of this study was to investigate this.

## Materials and Methods

The participants, intervention, comparisons, and outcome (PICO) for this meta-analysis were as follows: P: human (children, adults, regardless of health status); I: intake of omega-3 LC-PUFA supplements (any formulation, including capsules, tablets, syrups, etc.) or a diet rich in omega-3 LC-PUFAs; C: placebo, standardized diet, or no intake; and standardized diet, or no intake; and O: whether omega-3 LC-PUFA intake is effective in improving sleep quality. This study was conducted in accordance with the Priority Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines.[30] The protocol used to conduct this systematic review and meta-analysis is registered in the UMIN Clinical Trials Registry (registration number UMIN000052527).

**Eligibility criteria.** Studies considered eligible for this work included clinical trials with the following study design: (1) statistical analysis involving significance tests on the study results; (2) a study group with the intake of omega-3 LC-PUFAs; (3) a control group with no intake of omega-3 LC-PUFAs; (4) reported in a peer-reviewed original paper, written in English or Japanese; and (5) subjects were children or adults (regardless of health status). Exclusion criteria included (1) studies using interventions with multiple components to improve sleep in addition to

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omega-3 LC-PUFAs; and (2) studies of infants, whose sleep patterns are clearly different from those of children and adults.[31–33]

**Data collection process.** PubMed, The Cochrane Library, and Ichushi-web were used as databases for article searches. The search period was set to the entire period covered by each database. In PubMed, the search criteria were as follows: #1 "fish oils"[MeSH Terms] OR ("fish"[All Fields] AND "oils"[All Fields]) OR "fish oils"[All Fields] OR ("fish"[All Fields] AND "oil"[All Fields]) OR "fish oil"[All Fields]) OR "fish oil"[All Fields], #2 "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 "omega 3 fatty acid"[All Fields], #3 "sleep"[MeSH Terms] OR "sleep"[All Fields] OR "sleeping"[All Fields] OR "Sleeps"[All Fields] OR "sleeps"[All Fields] (#1 OR #2), AND #3. In Cochrane, searches were conducted for #1 fish oil, #2 fish, #3 omega-3 fatty acids, #4 sleep, (#1 OR #2 OR #3), AND #4. In Ichushi-web, searches were conducted on #1 (omega-3 fatty acids/TH or omega-3 fatty acids/AL), #2 n-3 fatty acids/AL, #3 (sleep/TH or sleep/AL), (#1 or #2), AND #3.

**Selection process and data collection process.**

*(1) Primary screening using abstracts.* With the exception of duplicate articles, the primary screening using abstracts excluded *in vivo* and *in vitro* studies, as well as clinical trials conducted for purposes unrelated to sleep-improving functions.

*(2) Secondary screening using the full text.* Articles that could not be judged from the abstracts were screened using the full text. Papers that did not meet the acceptance criteria were excluded. For each study, the following variables were extracted: author name, study country, subject characteristics, intervention, control, and intake period. Sleep efficiency, sleep latency, total sleep duration, and subjectively assessed sleep were collected as endpoints of this study. The data used in the meta-analysis are values after omega-3 LC-PUFA intake.

**Assessing risk of bias (RoB) and quality of evidence.** The quality of the included studies was assessed using the Cochrane Collaboration's Risk of Bias (RoB) Assessment Tool in the seven categories.[34] Each item was rated on a 3-point scale of "high", "low", and "unclear". Two reviewers independently evaluated the results, and if there were any discrepancies or questions in the evaluation results, the RoB was determined after discussion between the two reviewers. Egger's test was used as the method for testing publication bias,[35] with $p<0.1$ being set as significant. In cases of high heterogeneity, additional analyses were planned to search for possible causes. When omega-3 LC-PUFA were found to be effective for improving sleep quality, an analysis was performed using the leave-one-out method to assess robustness.[36,37]

**Synthesis methods.** For the synthesis of the results, we planned to evaluate them using forest plot, Q ($Chi^2$) and $I^2$ test in RevMan 5.4 when sufficient study data (mean, SD or SE, and number of subjects in each group) were available to perform a meta-analysis.[34] Egger's test was conducted using R4.3.1 with the packages "metafor".

As a statistical method for data integration, the "random effect model" was used because of the clear differences in subjects and protocols among studies, and the inverse variance method was used as the statistical method. The post-intake values were used to evaluate the results. Since the evaluation parameters were continuous variables, "mean difference" was used for sleep efficiency, sleep latency, and total sleep time, and for subjectively assessed sleep, standard mean difference was used because of the differences in the questionnaires used to assess this. Where standard errors were listed, they were converted to standard deviations. When only percentiles were mentioned in the article, they were converted to means and standard deviations using the method of Devore.[38] For articles that only stated the values of the amount of change and pre-intake value, an estimate of the post value was calculated with reference to the Cochrane handbook and used for the meta-analysis.[31] For total sleep duration, some papers did not provide a definition of this, but values with 'total sleep duration (or time)' were included in the meta-analysis. Also, for subjectively assessed sleep, only those with an overall sleep assessment value listed were included in the meta-analysis.

**Certainty assessment.** We assessed the certainty of evidence according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE).[39] Certainty was evaluated in five categories: (1) RoB, (2) indirectness, (3) imprecision, (4) inconsistency, and (5) other considerations (e.g., publication bias). Each included study was rated on a 3-point scale of very serious, serious, or not serious, and the certainty of evidence was rated on a 4-point scale of high (A), medium (B), low (C), or very low (D). The two reviewers conducted their evaluations independently, and in cases where there were differences or questions in the evaluation results, certainty was determined through discussions between the two reviewers.

## Results

**Study selection.** The search strategy resulted in the identification of 1,172 studies, 46 of which were duplicates. After primary screening, 1,133 studies were excluded, and after secondary screening of 39 studies, 8 studies were selected after obtaining the full text and thoroughly reviewing whether they met the eligibility criteria.[27–29,40–44] These are shown in Fig. 1.

**Study characteristics.** The data of each included study are presented in Table 1. The results of the bias risk assessment for each study are described in Fig. 2.

**Results of syntheses.**

*Sleep efficiency.* Of the five included studies that evaluated sleep efficiency, six items from five studies had post-intake values. Patan *et al.*[28] conducted a three-group study involving the intake of DHA-rich capsules, EPA-rich capsules, or placebo. The results of the analysis are shown in Fig. 3A using a forest plot and they indicate a significant effect on sleep efficiency {mean difference (MD) = 1.88, [95% confidence interval (CI) 1.00, 2.77], Z = 4.16, $p<0.0001$}. As for the test of heterogeneity, Q ($Chi^2$) = 3.05, $p = 0.69$, and $I^2 = 0\%$, confirming that there was low heterogeneity (defined as $I^2 = 0$–$40\%$).[34] Based on the above, we concluded that omega-3 LC-PUFAs are effective for improving sleep efficiency.

*Sleep latency.* Of the five included studies that evaluated sleep latency, six items from five studies had post-intake values. Similar to the above, the study by Patan *et al.*[28] involved three groups. The results of the meta-analysis are shown in Fig. 3B using a forest plot. The results showed that Z = 1.03, $p = 0.30$, and MD = −0.44 (95% CI −1.27, 0.39), indicating no significant effect. The result of the test for heterogeneity was Q ($Chi^2$) = 8.46, $p = 0.13$, and $I^2 = 41\%$, confirming moderate heterogeneity (defined as $I^2 = 30$–$60\%$).[34] Based on the above, it was determined that heterogeneity had some influence on the synthesis results, and we judged that omega-3 LC-PUFAs do not have a significant effect on sleep latency.

*Total sleep duration.* Of the four included studies that evaluated total sleep time, five items from four studies had post-intake values. Similar to the above, the study by Patan *et al.*[28] involved three groups. The results of the meta-analysis are shown in Fig. 3C using a forest plot. The results showed that Z = 0.68, $p = 0.50$, and MD = 5.45 (95% CI −10.33, 21.23), indicating no significant effect. As for the results from the test of heterogeneity, Q ($Chi^2$) = 9.85, $p = 0.04$, and $I^2 = 59\%$, confirming the possibility that there is moderate heterogeneity ($I^2 = 30$–$60\%$).[34] Based on the above, it was determined that heterogeneity had some influence on the synthesis results, and we judged that omega-3 LC-PUFAs do not have a significant effect on total sleep duration.

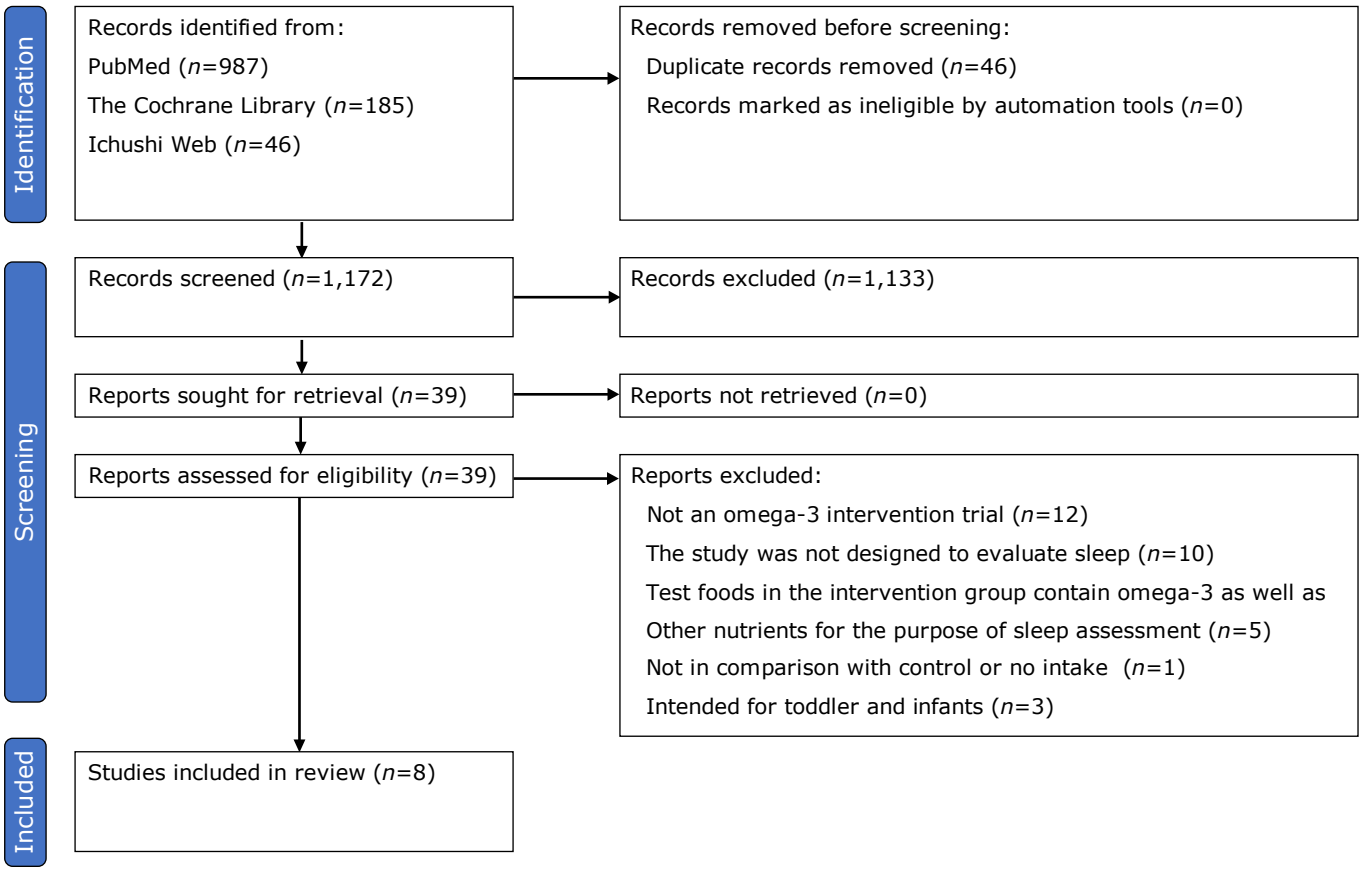


**Fig. 1.** Diagram of the study flow.

*Subjectively assessed sleep.* Of the four included studies in which the overall evaluation of sleep involved a subjective sleep assessment, six items from four studies with post-intake values were found. Two studies each had subjective results with two overall subjective sleep assessments.[41,42] The results of the meta-analysis are shown in Fig. 3D using a forest plot. The results showed $Z = 2.28$, $p = 0.02$, and MD = −0.41 (95% CI −0.76, −0.06), indicating a significant effect on subjectively assessed sleep. As for the results from the test of heterogeneity, Q ($Chi^2$) = 42.68, $p<0.00001$, and $I^2 = 88\%$, confirming the high heterogeneity (defined as $I^2 = 75–100\%$).[34] Given the above, we decided to conduct a subgroup analysis based on different omega-3 intake levels to investigate the causes of the high heterogeneity. With sleep as the primary endpoint, the lowest omega-3 intake at which an effect on sleep was observed was 600 mg DHA/day. Excluding the study by Purzand *et al.*,[43] which featured a lower omega-3 intake and an exceptionally positive effect of it on sleep, we found heterogeneity results of Q ($Chi^2$) = 5.43, $p = 0.25$, and $I^2 = 26\%$, confirming that there was low heterogeneity (defined as $I^2 = 0–40\%$).[34] The subgroup synthesis results of the meta-analysis are shown in Fig. 3E using a forest plot. For the synthesis results, $Z = 3.14$, $p = 0.03$, and MD = −0.16 (95% CI −0.30, −0.01), indicating that omega-3 LC-PUFAs are effective for improving subjectively assessed sleep.

**Reporting biases.** The results of the examination of publication bias are shown using funnel plots (Supplemental Fig. 1*). The results revealed mild visual asymmetry, and we confirmed it by Egger's test all results were $p>0.1$ (sleep efficiency: $p = 0.20$, sleep latency: $p = 0.74$, total sleep duration: $p = 0.71$, and objectively assessed sleep: $p = 0.89$),[35] and we judged the risk of reporting bias to be low.

**Certainty of evidence.** Based on the GRADE assessment,[39] the risks of bias, indirectness, imprecision, inconsistency, and other considerations (publication bias) were assessed for each outcome. The certainty of evidence for sleep efficiency and subjectively assessed sleep, which showed a significant effect of synthesis, is presented below.

*Sleep efficiency.* Regarding blindness bias, one study was found in which the blindness could not be confirmed because of fish and meat intake.[41] However, Hansen *et al.*[41] used a device to measure sleep efficiency, which is an outcome that is not affected by blinding considerably. Regarding other risks of bias, there are three studies with conflict of interest (COI) concerns (funded by a company that deals with the omega-3 ingredient). Based on the above, the overall RoB was judged to be "medium (−1)". Indirectness was determined to be "low (0)" because there were no factors that had a significant impact on the results of the study. The imprecision was rated as "medium ( −1)" because the number of subjects was less than 400 subjects although there were multiple reports in the study. Regarding inconsistency, heterogeneity was low ($I^2 = 0\%$), and the results of additional analysis using the leave-one-out method showed that the integration effect was consistently significant, ranging between 1.77 [0.85, 2.69] and 2.07 [0.95, 3.18] when any one data was excluded (Supplemental Table 1*). Because of the low heterogeneity and high robustness of the results, we evaluated the inconsistency as "low (0)". Publication bias was rated as "low (0)" because no significant difference was found in the meta-analysis test for publication bias (Egger's test). Based on the above results, we rated the certainty of evidence for sleep efficiency as B (medium).

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**Table 1.** Overview characteristics of the included studies

| No. | Study | Country | Participants | Intervation | Control | Duration | Sleep outcome |
|---|---|---|---|---|---|---|---|
| 1 | Doornbos *et al.* (2009) | Netherlands | Healthy pregnant women (*n* = 119) | 220 mg/day of DHA | Soybean oil | Week 16 pregnancy till 3 months postpartum | Sleep efficiency, Sleep duration |
| 2 | Hansen *et al.* (2014) | Norway | Male forensic patients aged 21–60 years (*n* = 95) | 300 g of Atlantic salmon containing 4.8 g of EPA+DHA was served three times a week and 150 g of salmon were served each time during the final 4 week of the study. | Meat (e.g., chicken, pork, beef) meals | 6 months | Sleep efficiency, Sleep latency, Sleep duration, Subjective assessment (Sleep quality score and Daily functioning score) |
| 3 | Montgomery *et al.* (2014) | UK | Healthy children aged 7–9 years (*n* = 362) | Capsules containing a total of 600 mg/day of DHA | Capsules containg corn oil or soy bean oil | 16 weeks | Sleep efficiency, Sleep latency, Sleep duration, Subjective assessment (Child Sleep Habits Questionnaire scores) |
| 4 | Cohen *et al.* (2014) | USA | Women aged 40–62 years experiencing the menopausal or postmenopausal transition (*n* = 355) | Fish oil capsule containing a total omega-3 dose of 615 mg, including EPA 425 mg and DHA 100 mg, along with other assorted omega-3 PUFA (90 mg) | Capsules containg olive oil | 12 week | Subjective assessment (Insomnia severity index and Pittsburgh Sleep Quality index) |
| 5 | Purzand *et al.* (2020) | Iran | Postmenopausal women aged 45–60 years (*n* = 180) | Capcules containing 1,000 mg of omega-3 fatty acid (180 mg of EPA and 120 mg of DHA per day) | Not described | 12 week | Subjective assessment (Sleep problems) |
| 6 | Patan *et al.* (2021) | UK | Healthy adults aged between 25–49 years (*n* = 90) | The DHA-rich capsules provided 900 mg of DHA and 270 mg of EPA per day, the EPA-rich capsules provided 360 mg of DHA and 900 mg of EPA per day | Capsules containg olive oil | 26 week | Sleep efficiency, Sleep latency, Sleep duration |
| 7 | Vuholm *et al.* (2021) | Denmark | Healthy children aged 8 or 9 years (*n* = 199) | A weekly intake of about 300 g of oily fish, which was expected to provide approximately 0.8–1.0 g/day of omega-3 LC-PUFA. | Frozen, organic chicken and a variety of cold poultry lunch products such as chicken liver pate, poultry sausages and chicken meatballs. | 12 week | Sleep latency, Sleep duration |
| 8 | Yokoi-Shimizu *et al.* (2022) | Japan | Healthy Japanese adults aged ≥45 years with poor sleep quality (*n* = 66) | Fish oil capsules containing 576 mg of DHA and 284 mg of EPA per day | Capsules containg corn oil | 12 week | Sleep efficiency, Sleep latency, Sleep duration |

*Subjective sleep assessment.* Regarding blindness bias, one study was found in which the blindness could not be confirmed because of fish and meat intake.[41] Regarding other risks of bias, there are one study with COI concerns (funded by a company that deals with the omega-3 ingredient). Based on the above, the overall RoB was judged to be "medium (−1)". Indirectness was rated "medium (−1)" because two of the studies did not have sleep effects as a primary endpoint. The imprecision was rated as "low (0)" because the number of subjects was more than 400 subjects and there were multiple reports in the study. Regarding inconsistency, heterogeneity $I^2 = 88\%$, which confirmed a considerably high heterogeneity, and we considered that the subgroup analysis by amount of omega-3 intake would have identified the cause of the heterogeneity. The results of the analysis using the leave-one-out method confirmed that the robustness of the synthesis effect was not very high, as the synthesis effect was not significant in the meta-analysis only when the study by Cohen *et al.*[42] was excluded. For these reasons, we rated the inconsistency as "medium (−1)". Other biases were rated "low (0)" because no significant difference was found in Egger's test for publication bias. Based on the above results, we rated the certainty of evidence for subjective sleep assessment as "B (medium)".

Details of all assessments, including sleep latency and total sleep duration, are presented in Table 2.

## Discussion

The purpose of this review was to systematically examine the relationship between omega-3 LC-PUFA supplementation and sleep by conducting a meta-analysis of the effects of such supplementation on sleep efficiency, sleep latency, total sleep duration, and subjectively assessed sleep. The overall results of this study indicate that omega-3 LC-PUFA intake significantly improved sleep efficiency and subjectively assessed sleep compared with those in the control group.

A meta-analysis of omega-3 and sleep conducted by Dai *et al.*[12] concluded that the intake of omega-3 LC-PUFAs may improve some aspects of sleep and reduce total sleep disturbance scores in infants, with no effect observed in children or adults. Four of the eight studies included in this study were published after this report by Dai *et al.*,[12] allowing a more reliable meta-analysis and providing the present results. With the increasing importance of improving sleep quality worldwide and more studies being conducted on this topic each year, more studies will be added in

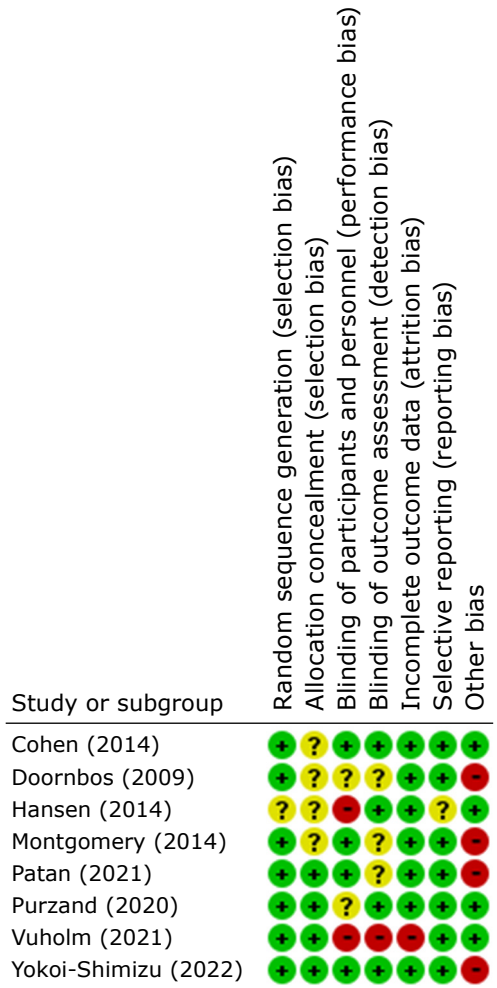


**Fig. 2.** Assessment of RoB for eight included studies: summary of items of bias. RoB for all trials is presented as low (green), high (red), or unclear (yellow) RoB in each assessment item. See color figure in the on-line version.

the future and more reliable meta-analyses can be conducted.

In the present study, sleep efficiency was the only objective outcome for which omega-3 LC-PUFAs were found to be effective. The reason for this is that sleep efficiency is calculated as the ratio of actual sleep time to the time spent sleeping, and actual sleep time decreases as the time spent awake in the middle of sleep increases, resulting in a decline of sleep efficiency. Therefore, only sleep efficiency, differing from sleep latency and total sleep time, is related to amount of time spent awake. We hypothesized that omega-3 was only observed to have an effect on sleep efficiency because omega-3 LC-PUFAs were found to be effective in reducing the amount of time spent awake. A meta-analytic evaluation of three of the included studies with values for the amount of time awake confirmed that omega-3 LC-PUFA intake significantly reduced the amount of time awake [$Z = 3.21$ ($p = 0.001$),[28,29,42] MD = −7.46 (95% CI −12.01, −2.91), $Q(Chi^2) = 2.15$, $p = 0.54$, $I^2 = 0\%$] (Supplemental Fig. 2*). In a study by Yokoi-Shimizu *et al.*,[29] the Oguri-Shirakawa-Azumi (OSA) sleep inventory middle-age (MA) version,[48] which was used for subjectively assessing sleep, showed a significant effect of omega-3 LC-PUFAs only on frequent dreaming among the five factors (sleepiness on rising, initiation and maintenance of sleep, frequent dreaming, refreshing, and sleep length) that can be assessed with OSA. These findings suggest that omega-3 LC-PUFAs may have an effect on reducing the amount of time spent awake. The causes of increased wakefulness in the middle of the night include alcohol consumption, insomnia, nocturia, psychiatric disorders such as depression, and sleep apnea,[49] but the most significant factor is thought to be stress.[50–52] In addition, when stress causes disturbances in the balance between sympathetic and parasympathetic autonomic nervous systems, it becomes difficult to fall asleep and maintain sleep, resulting in intermittent and shallow sleep, which is thought to cause awakenings in the middle of the night when noises or changes in room temperature occur.[53–55] Omega-3 LC-PUFAs have also been proven effective in regulating the balance between sympathetic and parasympathetic nervous systems in several studies, and meta-analyses have confirmed their effectiveness.[56] In the studies included in this meta-analysis, Hansen *et al.*[41] also measured heart rate variability before and after supplementation and found that only the omega-3 LC-PUFA ingestion group had increased high-frequency (HF) power during sleep. HF power is considered an indicator of parasympathetic activity,[57,58] and omega-3 LC-PUFA intake was found to increase parasympathetic activity during sleep. As to the mechanism by which omega-3 LC-PUFAs affect sleep, several studies have identified the regulatory effect of melatonin production as a mechanism. Melatonin is a hormone secreted by the pineal gland that plays an important role in regulation of the autonomic nervous system.[59,60] Several animal studies have reported that omega-3 fatty acids are present as component lipids of all cell membranes in the body and that ingestion may modulate melatonin production by altering the membrane phospholipid composition of the pineal gland,[61–64] which produces melatonin.[65,66] This suggests that omega-3 may improve sleep efficiency by regulating the balance of the autonomic nervous system through the regulation of melatonin production and reducing awakening during sleep.

In the studies included in this meta-analysis, sleep efficiency, sleep latency, and total sleep duration were measured using sleep measurement devices or a questionnaire about sleep.[40] Sleep measurement devices include a wristwatch and mat-type devices that calculate sleep status by comprehensively evaluating blood pressure,[45,46] body movement, respiration, and other factors. The data obtained through the sleep diary used in the study by Doornbos *et al.*[40] have been confirmed to correlate with sleep measurement devices and were considered acceptable for inclusion in the meta-analysis.[47]

Among the eight studies included in this work, the subjects were adults in six studies and children in two.[27,44] Regarding sleep in infants and children/adults, according to the sleep structure examined by polysomnography, in infants under 1 year of age, about half of the daily sleep is rapid eye movement (REM) sleep until about 1 month after birth. After that time, the percentage of REM sleep decreases rapidly, reaching about 20% by the time the infant is 3 years old, almost the same level as that of adults.[31,32] In other words, we considered that the sleep pattern remains unchanged above the age of 3 years. Regarding sleep duration, the National Sleep Foundation in the U.S. recommends that infants aged 0–3 months get 14–17 h of sleep, based on a range of data and various studies on sleep and health, and that their sleep duration differs from that of adults.[33] This meta-analysis confirmed the beneficial effect of omega-3 on sleep efficiency, and an analysis of only studies in adults similarly showed a positive effect of omega-3. [$Z = 3.82$, $p = 0.0001$, MD = 1.77 (95% CI 0.86, 2.67)]. For subjective assessment, a stratified analysis of only adults, excluding the study by Purzand *et al.*,[43] showed a beneficial effect of omega-3 [$Z = 2.10$, $p = 0.04$, MD = −0.20, 95% CI (−0.40, −0.01)]. Thus, the effects of omega-3 on sleep efficiency and subjectively assessed sleep were similarly confirmed when stratified analysis was performed for adults only. The amount of omega-3 consumed in the adopted studies ranged from 220 to 2,060 mg/day of omega-3 LC-PUFAs, and the amount of omega-3 LC-PUFAs that had an effect on sleep ranged

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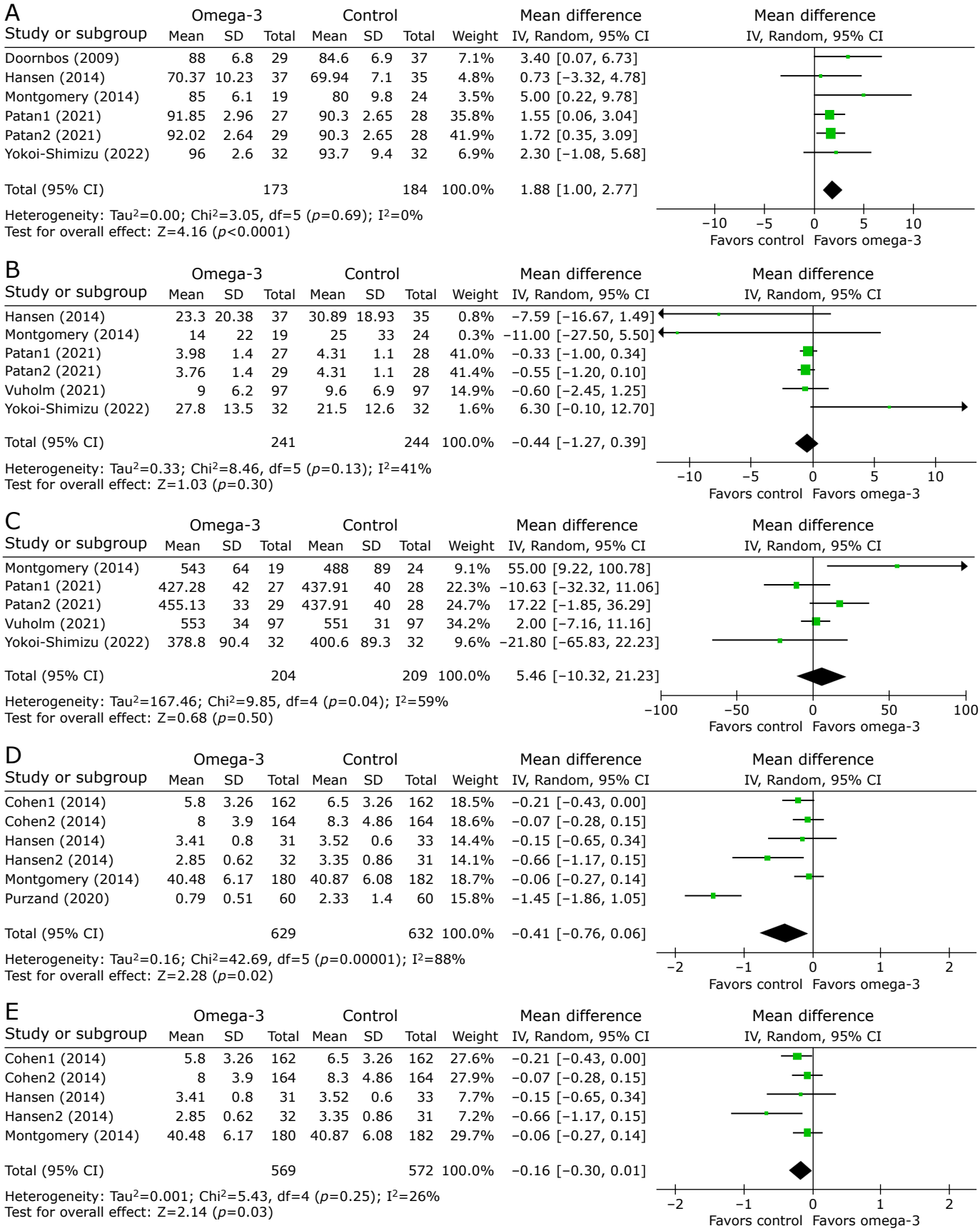


**Fig. 3.** Synthesis effects of omega-3 long-chain polyunsaturated fatty acids on sleep outcomes. (A) sleep efficiency (%), (B) sleep latency (min), (C) total sleep duration (min), (D) subjectively assessed sleep, and (E) subjectively assessed sleep subgroup analysis.

**Table 2.** Certainty of evidence

| Outcomes | Certainty of assessment | | | | | | | Certainty |
|---|---|---|---|---|---|---|---|---|
| | Number of studies | Participants (*n*) | Risk of bias | Indirectness | Imprecision | Inconsistency | Other consideration | |
| Sleep efficiency | 5 | 329 | Serious[a,c] | Not serious | Serious | Not serious[g] | Not serious[k] | B (medium) |
| Sleep latency | 5 | 457 | Serious[a,c] | Not serious | Not serious[f] | Serious[h] | Not serious[k] | B (medium) |
| Total sleep duration | 4 | 385 | Serious[a,c,d] | Not serious | Serious | Serious[i] | Not serious[k] | C (low) |
| Subjective sleep assessment | 4 | 875 | Serious[b,c] | Serious[e] | Not serious[f] | Serious[j] | Not serious[k] | B (medium) |

[a]Blinding was not confirmed in the included studies, but they used a device for measurement, an outcome that is not significantly affected by blinding. [b]Blinding was not confirmed in the included studies. [c]Included studies with conflict of interest (COI) concerns (funded by a company that deals with omega-3 ingredients). [d]One study for which the reason for the attrition was not stated. [e]Two of the studies did not have sleep effects as a primary endpoint. [f]The number of subjects was more than 400 and there were multiple reports in the study. [g]$I^2 = 0\%$, Leave-one-out method showed that the integration effect was consistently significant. [h]$I^2 = 41\%$, [i]$I^2 = 59\%$, [j]$I^2 = 88\%$, Leave-one-out method confirmed that the robustness of the synthesis effect was not very high. [k]No significant difference was found in Egger's test for publication bias.

from 300 to 2,060 mg/day. In studies in which sleep was evaluated as the primary endpoint, effectiveness was found in the range of 600 to 2,060 mg of omega-3 LC-PUFAs. The duration of intake ranged from 12 weeks to about 9 months, and there were no studies with shorter durations of intake. Since omega-3 LC-PUFAs often exert their effects by inserting themselves into cell membranes after ingestion,[61–64] we considered it reasonable that the effects were confirmed when the consumption period was 12 weeks or longer.

For the subjective assessment of sleep, various assessment items were used in the studies included in this meta-analysis: the Insomnia Severity Index and the Pittsburgh Sleep Quality Index by Cohen *et al.*,[42,67–69] Child Sleep Habits Questionnaire scores by Montgomery *et al.*,[27,70] sleep quality score[71] and daily functioning score by Hansen *et al.*,[41] and sleep problems by Purzand *et al.*.[43] Patan *et al.*[28] and Yokoi-Shimizu *et al.*[29] also conducted subjective assessments, but they were not used in the present study because they did not involve comprehensive assessments of sleep. The OSA sleep inventory MA version used by Yokoi-Shimizu *et al.*[29,48] for subjective evaluation is categorized into five factors (sleepiness on rising, initiation and maintenance of sleep, frequent dreaming, refreshing, and sleep length) and does not have an assessment index for overall evaluation. Patan *et al.*[28] used the visual analog scale (VAS) for responses to questions about various states of sleep, with no results assessing overall sleep status. Since there are various measures for the subjective assessment of sleep, standardized mean difference was used to evaluate it, but additional analysis was performed because heterogeneity was very high with $I^2 = 88\%$. Purzand *et al.*[43] used sleep as a secondary endpoint in their study of menopause, and although their intake of DHA/EPA of 300 mg/day was the lowest among the studies in this meta-analysis, the effect of omega-3 was extraordinarily high. In addition, studies that evaluated sleep as the primary endpoint showed a benefit from 600 mg of omega-3 (DHA/EPA), and the study by Purzand *et al.*[43] was judged to be of low quality and unreliable. Upon excluding that study, heterogeneity was $I^2 = 26\%$, indicating the effectiveness of omega-3 LC-PUFAs in subjective sleep assessment.

Six studies included in this work used sleep as the primary endpoint, and two evaluated only secondary endpoints. For two reports,[42,43] the subjects were peri- and postmenopausal women, and subjective assessment of sleep was also included in the assessment of menopause. These two studies were included only in the meta-analysis of subjectively assessed sleep, which reduced the certainty of the evidence. For sleep efficiency, sleep latency, and sleep duration, we evaluated only those studies in which sleep was the primary endpoint, and we took this into consideration in our evaluation of the certainty of the evidence. To include a wide range of studies on omega-3 and sleep, we also included studies that evaluated sleep with secondary endpoints. However, we still believe that the quality of the results of subjectively assessed sleep will vary between studies that focus mainly on sleep and those that do not, so if more intervention studies on omega-3 and sleep are conducted in the future, it may be possible to conduct a meta-analysis employing only studies with sleep as the primary endpoint. None of the eight included studies involved the consumption of experimental diets containing alpha-linolenic acid as the main ingredient of omega-3 LC-PUFAs, and all of them involved the consumption of EPA and DHA as the main ingredients. Therefore, this study can be considered a meta-analysis of studies in which the effects of EPA and DHA, among other omega-3s, were observed. Although α-linolenic acid is known to have low conversion efficiency, it is known to be converted to EPA and DHA at a conversion rate of about 5%.[72,73] Based on the present results to achieve optimal effects on sleep, it is considered better to consume seafood and supplements rich in EPA and DHA than diets and supplements rich in α-linolenic acid.

The limitations of the results in this study include the differences in the health status of the subjects, psychological factors, and the duration and amount of intake from each study. In addition, studies that did not use sleep evaluation as the primary endpoint were also included, and the measures for evaluating subjective evaluation items varied. Moreover, although they were evaluated using standardized mean differences, they could not be validated using the same evaluation measures. The number of included studies was eight, which is not sufficient. Additionally, since the selection process for this research review included only studies reported in English or Japanese, the existence of other relevant studies reported in other languages cannot be ruled out, and the possibility of a bias related to language cannot be overlooked.

This study evaluated the effects of omega-3 LC-PUFAs on sleep quality via a meta-analysis. Sleep efficiency, sleep latency, sleep duration, and subjectively assessed sleep were set as endpoints, and the possibility of omega-3 LC-PUFAs affecting sleep efficiency and subjectively assessed sleep was considered. The results revealed that omega-3 LC-PUFAs may improve sleep quality. The number of studies on omega-3 LC-PUFAs and sleep has increased over the years, but we believe that further evaluation of this issue is needed in the future.

## Author Contributions

KS performed study conception and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, and statistical analysis. YK assessed the quality of evidence and performed certainty assessment. KH studied the study concept and design, and supervised the study.


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## Abbreviations

| | |
|---|---|
| CI | confidence interval |
| DHA | docosahexaenoic acid |
| EPA | eicosapentaenoic acid |
| GRADE | Grading of Recommendations Assessment, Development and Evaluation |
| HF | high frequency |
| LC-PUFA | long-chain polyunsaturated fatty acid |
| MD | mean difference |
| PICO | participants, intervention, comparisons, and outcome |
| PRISMA | Priority Reporting Items for Systematic Reviews and Meta-Analyses |
| REM | rapid eye movement |
| RoB | risk of bias |
| VAS | visual analog scale |

## Conflict of Interest

No potential conflicts of interest were disclosed.

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