A meta-analysis of the analgesic effects of omega-3 polyunsaturated fatty acid supplementation for inflammatory joint pain

Robert J. Goldberg [a,c], Joel Katz [a,b,c,d,*]

[a] Department of Psychology, York University, Toronto, ON, Canada
[b] School of Kinesiology and Health Science, York University, Toronto, ON, Canada
[c] Department of Anesthesia and Pain Management, Toronto General Hospital and Mount Sinai Hospital, Canada
[d] Department of Anesthesia, University of Toronto, Canada

Abstract

Between 40% and 60% of Americans use complementary and alternative medicine to manage medical conditions, prevent disease, and promote health and well-being. Omega-3 polyunsaturated fatty acids (ω-3 PUFAs) have been used to treat joint pain associated with several inflammatory conditions. We conducted a meta-analysis of 17 randomized, controlled trials assessing the pain relieving effects of ω-3 PUFAs in patients with rheumatoid arthritis or joint pain secondary to inflammatory bowel disease and dysmenorrhea. Meta-analysis was conducted with Cochrane Review Manager 4.2.8. for six separate outcomes using standardized mean differences (SMDs) as a measure of effect size: (1) patient assessed pain, (2) physician assessed pain, (3) duration of morning stiffness, (4) number of painful and/or tender joints, (5) Ritchie articular index, and (6) nonselective nonsteroidal anti-inflammatory drug consumption. Supplementation with ω-3 PUFAs for 3–4 months reduces patient reported joint pain intensity (SMD: −0.26; 95% CI: −0.49 to −0.03, $p = 0.03$), minutes of morning stiffness (SMD: −0.43; 95% CI: −0.72 to −0.15, $p = 0.003$), number of painful and/or tender joints (SMD: −0.29; 95% CI: −0.48 to −0.10, $p = 0.003$), and NSAID consumption (SMD: −0.40; 95% CI: −0.72 to − 0.08, $p = 0.01$). Significant effects were not detected for physician assessed pain (SMD: −0.14; 95% CI: −0.49 to 0.22, $p = 0.45$) or Ritchie articular index (SMD: 0.15; 95% CI: − 0.19 to 0.49, $p = 0.40$) at 3–4 months. The results suggest that ω-3 PUFAs are an attractive adjunctive treatment for joint pain associated with rheumatoid arthritis, inflammatory bowel disease, and dysmenorrhea.

1. Introduction

Between 40% and 60% of Americans use complementary and alternative medicine to manage medical conditions, prevent disease, and promote health and well-being (Astin, 1998; Barnes et al., 2004). Not surprisingly, 33% of those who use complementary medicine cite pain as the primary reason (Barnes et al., 2004). Dietary constituents and supplements used as potential therapeutic agents for the treatment of pain include dietary soy, omega-3 polyunsaturated fatty acids (ω-3 PUFAs), sucrose, and anthocyanins found in tart cherries and other fruits and vegetables with highly colored pigments (Tall and Raja, 2004). With one exception, there is little in the way of empirical evidence to support the safe and effective use of dietary supplements for managing pain. The exception is the ω-3 PUFAs; controlled trials demonstrate their efficacy in reducing joint pain associated with inflammatory conditions, including rheumatoid arthritis (RA), inflammatory bowel disease, and dysmenorrhea.

* Corresponding author. Address: Department of Psychology, BSB 232, York University, 4700 Keele Street, Toronto, ON, Canada M3J 1P3. Tel.: +416 736 2100x40557; fax: +416 736 5814.
E-mail address: jkatz@yorku.ca (J. Katz).

Concern over gastrointestinal bleeding and myocardial infarction associated with nonselective nonsteroidal anti-inflammatory drugs (NSAIDs) (Langford, 2006) and selective cyclooxygenase-2 (COX-2) inhibitors (Andersohn et al., 2006) has prompted the search for other treatments for chronic inflammatory pain. Dietary supplementation with long-chain ω-3 PUFAs, eicosapentaenoic acid (EPA) (20:5ω-3), and docosahexaenoic acid (DHA) (22:6ω-3), may be an effective adjunct to NSAID therapy (Albert et al., 2005; Calder, 2006). The typical North American diet is very low in EPA and DHA (MacLean et al., 2004) and conversion is limited from dietary α-linolenic acid, found in vegetable oils, to EPA and DHA (James et al., 2003).

Fish oil is a rich source of long-chain ω-3 PUFAs, typically containing 18% EPA and 12% DHA derived from marine fish (Cleland et al., 2006). In humans, supplementation with fish oil, or EPA/DHA capsules, increases the incorporation of ω-3 PUFAs into phospholipids (James et al., 2003), conferring anti-inflammatory effects (Stamp et al., 2005; Calder, 2006). Early studies reviewed by Stamp et al. (2005) and Calder (2006) attributed these anti-inflammatory effects to competition with arachidonic acid for production of inflammatory eicosanoids. More recent investigations show that EPA and DHA produce novel anti-inflammatory lipids (i.e., resolvins and protectins) which appear, in a transgenic mouse model, to have anti-inflammatory effects (Arita et al., 2005; Lukiw et al., 2005; Hudert et al., 2006). Transgenic mice engineered to overexpress *fat-1*, an ω-3 desaturase from roundworms, overproduce ω-3 PUFAs, resolvins and protectins. These mice are protected from dextran sulphate-induced colitis, a standard model of inflammation, but no change in the levels of ω-6 PUFA-derived prostaglandin E_2 (PGE_2) or leukotriene B_4 (LTB_4) was observed, indicating competition between ω-3 PUFAs and arachidonic acid is not important in this model (Hudert et al., 2006). Through these, and possibly other mechanisms, EPA and DHA inhibit activation of the transcription factor nuclear factor κB (NF-κB), and the release of the cytokines interleukin-1 beta (IL-1β) and tumor necrosis factor α (TNF-α), central regulators of inflammation (Fig. 1) (Novak et al., 2003; Zhao et al., 2004; Chen et al., 2005; De Caterina and Massaro, 2005; Stamp et al., 2005; Calder, 2006; Hudert et al., 2006).

The objective of the present review is to conduct a meta-analysis examining the pain relieving effects of EPA/DHA in patients with RA or joint pain secondary to inflammatory bowel disease or dysmenorrhea.

2. Methods

We followed the Quality of Reporting of Meta-analyses (QUORUM) guidelines for reporting meta-analyses of randomized controlled trials (Moher et al., 1999).
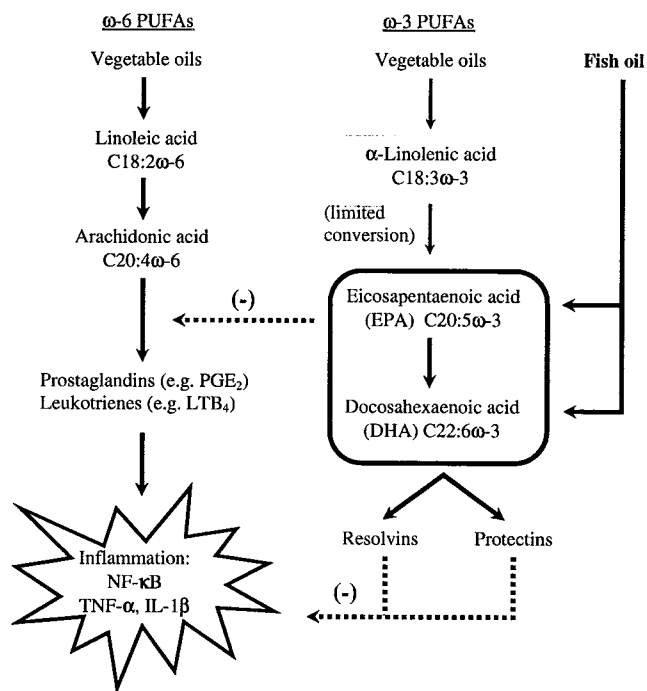

Fig. 1. Metabolism of inflammatory mediators from ω-6 PUFAs and sites of inhibition by ω-3 PUFAs.

2.1. Identification of trials and inclusion criteria

The following databases were searched for entries up to November 2006: MEDLINE, EMBASE, CINAHL (Cumulative Index to Nursing & Allied Health Literature), Ovid Healthstar and AMED (Allied and Complementary Medicine). The following key words were used in the search strategy: ((omega-3 *or* n-3 *or* "fish oil" *or* eicosapentaenoic *or* epa *or* docosahexaenoic *or* dha) *and* ("rheumatoid arthritis" *or* "inflammatory bowel disease" *or* IBD *or* dysmenorrhea)). The search was limited to English language publications and randomized clinical trials. References from relevant articles were checked for further studies.

2.2. Outcomes of interest and rationale for pooling studies

An assessment of pain was operationalized as any direct measure or index of joint pain, joint tenderness, or joint stiffness. Direct measures and indices of inflamed tissue (e.g., swollen joint counts) were not considered assessments of pain (joint swelling and tenderness are not significantly correlated (Prevoo et al., 1993)). Six different pain outcomes were identified: (1) patient assessed pain (visual analog scale (VAS) or categorical scale), (2) physician assessed pain (VAS or categorical scale), (3) duration of morning stiffness (minutes or hours), (4) number of painful and/or tender joints, (5) Ritchie articular index, a tool for assessing joint tenderness elicited from the application of pressure over the joint margin of articular joints (Ritchie et al., 1968), and (6) NSAID consumption.

All studies included in the final meta-analysis employed a randomized design, and compared patients receiving ω-3 PUFAs relative to an inert substance. Studies manipulating

analgesic consumption during the treatment period were excluded. Pain outcomes were considered separately, and not pooled, so as to limit clinical heterogeneity.

2.3. Data extraction and assessment of quality and validity

A data extraction process was performed on the articles that met inclusion criteria. The following items were collected: publication details, duration of study, patient population, sample size, dosage of ω-3 PUFA supplements, total dosage of ω-3 PUFA supplements, type of placebo, and type of NSAID administered.

Methodological quality was measured independently by two reviewers (RJG and JK) using the Jadad quality index scale (Jadad et al., 1996). The scale uses a six point (0–5) rating system (in which lower quality articles receive lower scores) to assess the likelihood of bias in pain research reports based on descriptions of randomization, blinding, and withdrawals. Validity was scored independently by the same two reviewers using the 0–16 point Oxford Pain Validity Scale (Smith et al., 2000). Articles with lower validity receive lower scores on the Oxford Pain Validity Scale.

The two reviewers were blinded to the authors, institutions, addresses, acknowledgements, and publication details when rating the quality and validity of each article. The quality and validity scores for articles included and excluded from analysis were compared using an independent samples t-test.

2.4. Statistical analysis

Meta-analysis was conducted with Cochrane Review Manager 4.2.8. (http://www.cc-ims.net/RevMan) for the six outcome measures using standardized mean differences (SMDs) as a measure of effect size. In order to include as many trials in the meta-analysis as possible, even when not all information was reported, means and standard deviations were estimated based on the median, range, and sample size (Hozo et al., 2005). Estimation was performed for three studies (Cleland et al., 1988; Tulleken et al., 1990; Nielsen et al., 1992).

Only the most conservative estimate of effect size was used when an outcome measure was reported at more than one time interval within a specified period (e.g., 9 and 12 months), or when two different measures of the same outcome measure were reported (e.g., patient assessed pain on a 10 cm VAS and a categorical scale). We calculated SMD instead of weighted mean differences (WMDs) since several pain outcomes (e.g., patient assessed pain) were assessed on different scales across the studies. Statistical heterogeneity was tested by Q test (χ^2) and reported with the I^2 statistic. Higher values of I^2 indicate higher heterogeneity. All meta-analyses were carried out with the random effects model.

A primary analysis was conducted for studies administering ω-3 PUFA supplementation for 3–4 months. Separate analyses were also conducted for studies administering supplementation for less than two months, and longer than 5 months. These three time intervals were based on previous reports suggesting that the therapeutic effects of ω-3 PUFAs are usually manifest after approximately 3 months (Stamp et al., 2005). We hypothesized that patients taking ω-3 PUFA supplementation for 2 months or less would not benefit significantly.

Articles were categorized based on dose of ω-3 PUFA intake (high-dose intake, low-dose intake), and the dietary supplement/placebo given to the control group (olive oil, non-olive oil). A daily ω-3 PUFA intake of 2.7 g was used to distinguish high-dose and low-dose ω-3 PUFA intake based on previous reports in RA which recommend a dose of 2.7–4.0 g per day of EPA and DHA combined (Stamp et al., 2005). For studies reporting outcomes at 3–4 months, subgroup analyses were performed based on dose of ω-3 PUFAs and type of placebo.

3. Results

3.1. Trials and patients

Our search strategy (Fig. 2) identified 24 articles (and one abstract (Darlington and Ramsey, 1987)) assessing the effects of dietary ω-3 PUFA supplementation on joint pain outcomes (Kremer et al., 1985; Kremer et al., 1987; Belch et al., 1988; Cleland et al., 1988; Magaro et al., 1988; Tulleken et al., 1988; Kremer et al., 1990; Tulleken et al., 1990; van der Tempel et al., 1990; Kjeldsen-Kragh et al., 1992; Nielsen et al., 1992; Skoldstam et al., 1992; Lau et al., 1993; Geusens et al., 1994; Kremer et al., 1995; Nordstrom et al., 1995; Hansen et al., 1996; Volker et al., 2000; Adam et al., 2003; Sampalis et al., 2003; Bjorkkjaer et al., 2004; Remans et al., 2004; Sundrarjun et al., 2004; Berbert et al., 2005). Two trials were excluded from the meta-analysis due to an experimental design involving concomitant supplementation of ω-3 PUFAs with NSAIDs followed
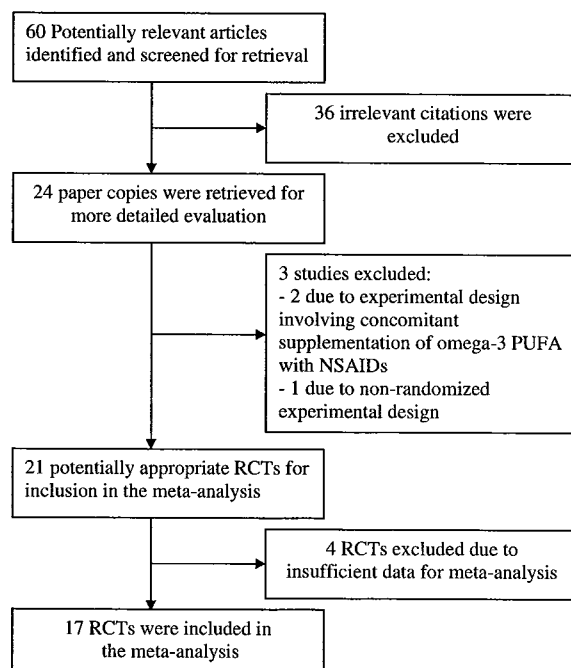
Fig. 2. Modified flow diagram of search strategy based on the QUORUM guidelines, RCTs = randomized controlled trials.

by a stepwise reduction in NSAID consumption over the duration of the study (Kjeldsen-Kragh et al., 1992; Kremer et al., 1995). A third trial was excluded due to a non-randomized design (Kremer et al., 1987). Four placebo-controlled studies were not included because they did not report sufficient data (Belch et al., 1988; Tulleken et al., 1988; Hansen et al., 1996; Volker et al., 2000).

Seventeen studies reporting sufficient data for meta-analysis (Table 1), with a total of 823 patients, were included in the final analysis. Six studies reported at least one pain outcome at two months or less, 16 reported at least one pain outcome at 3–4 months, and six studies reported at least one pain outcome at 5 months or longer. We did not include the results for morning stiffness and number of tender joints from one study (Bjorkkjaer et al., 2004) due to significant between group differences at baseline.

3.2. Outcome measures

3.2.1. Main analysis

A meta-analysis of 16 studies at 3–4 months (Kremer et al., 1985; Cleland et al., 1988; Kremer et al., 1990; Tulleken et al., 1990; van der Tempel et al., 1990; Nielsen et al., 1992; Skoldstam et al., 1992; Lau et al., 1993; Geusens et al., 1994; Nordstrom et al., 1995; Adam et al., 2003; Sampalis et al., 2003; Bjorkkjaer et al., 2004; Remans et al., 2004; Sundrarjun et al., 2004; Berbert et al., 2005) showed significant effects for four of six pain outcomes: patient assessed pain, morning stiffness, number of painful and/or tender joints, and NSAID consumption (Fig. 3). In contrast, significant effects were not detected for physician assessed pain and Ritchie articular index.

Patient assessed pain was reported in 19 studies at 3–4 months. Thirteen studies provided sufficient data for meta-analysis. Of these 13 studies, 2 found a significant improvement relative to placebo, seven noted an improvement in patients receiving ω-3 PUFAs that did not reach significance, and four reported no difference between ω-3 PUFAs and placebo. One study (Cleland et al., 1988) reporting a non-significant difference in patient assessed pain between ω-3 PUFAs and placebo groups reported a significant improvement in patient assessed pain in the olive oil group. Overall, patients receiving ω-3 PUFAs fared better than placebo for patient assessed pain (SMD: −0.26; 95% confidence interval [CI]: −0.49 to −0.03, $p = 0.03$). Of the six studies not reporting sufficient data for meta-analysis (Kremer et al., 1985; Belch et al., 1988; Lau et al., 1993; Hansen et al., 1996; Volker et al., 2000; Adam et al., 2003), three found a significant improvement relative to placebo, one found an improvement that favoured ω-3 PUFAs but did not reach significance, and two found no difference between groups.

Morning stiffness was reported in 16 studies at 3–4 months. Eight studies provided sufficient data for meta-analysis. Of these eight studies, two found a significant improvement relative to placebo, one found a significant improvement in the ω-3 PUFAs group relative to baseline, four reported an improvement in patients receiving ω-3 PUFAs that did not reach significance, and one did not find a difference. Overall, patients receiving ω-3 PUFAs fared better than placebo for morning stiffness (SMD: −0.43; 95% CI: − 0.72 to −0.15, $p = 0.003$). Among the eight studies not reporting sufficient data for meta-analysis (Belch et al., 1988; Tulleken et al., 1988; Skoldstam et al., 1992; Lau et al., 1993; Geusens et al., 1994; Hansen et al., 1996; Volker et al., 2000; Adam et al., 2003), three reported a significant improvement relative to placebo, and five found no difference between groups.

Number of painful and/or tender joints was reported in 11 studies at 3–4 months, 10 of which provided sufficient data for meta-analysis. Of these 10 studies, one found a significant improvement relative to placebo, two found a significant improvement in the ω-3 PUFA group relative to baseline (one of which also noted a significant, but less pronounced, improvement in the placebo group), five noted an improvement in patients receiving ω-3 PUFAs that did not reach significance, and two did not find any between group differences. Overall, patients receiving ω-3 PUFAs fared better than placebo for number of painful and/or tender joints (SMD: −0.29; 95% CI: −0.48 to − 0.10, $p = 0.003$). One study reporting insufficient data for meta-analysis (Volker et al., 2000) found a significant improvement relative to placebo.

NSAID consumption was reported in six studies at 3–4 months, three of which provided sufficient data for meta-analysis. Of these three studies, two found a significant decrease in NSAID use relative to placebo and one did not find any between group differences. Overall, patients receiving ω-3 PUFAs fared better than placebo for NSAID consumption (SMD: −0.40; 95% CI: −0.72 to − 0.08, $p = 0.01$). Among the three studies reporting insufficient data for meta-analysis (Belch et al., 1988; Kremer et al., 1990; Hansen et al., 1996), two found a significant improvement relative to placebo, and one did not find any between group differences.

Of the six studies reporting outcomes at 5 months or longer (Fig. 4), significant improvements were detected for two of the six pain outcomes: physician assessed pain (SMD: −0.50; 95% CI: − 0.98 to −0.01, $p = 0.05$) and number of painful and/or tender joints (SMD: −0.51; 95% CI: −1.00 to −0.02, $p = 0.04$). It is important to note that effect sizes among studies of ω-3 PUFA supplementation for 5 months or longer were generally larger than effect sizes at 3–4 months. However, due to the limited number of studies available and corresponding lack of statistical power, only two outcome measures

Table 1
Description of the 17 studies included in the meta-analysis

Study	Duration[a]	Patient population	n[b]	ω-3 PUFA supplement in treatment group[c]	Total ω-3 PUFA supplement in treatment group[c]	Type of placebo	Type of NSAID consumption	Quality score[d]	Validity score[e]
Berbert et al. (2005)	24 weeks	Rheumatoid arthritis	55	Twenty capsules of fish oil each containing 90 mg EPA and 60 mg DHA	3.0 g	Soy oil capsules	No differences between groups in NSAID consumption at start of study; NSAID consumption during study and type of NSAIDs not reported	2	5
Bjorkkjaer et al. (2004)	6 months	Rheumatic joint pain from inflammatory bowel disease	19	Ten milliliters of seal oil, three times daily providing a total of 2.0 g EPA, 0.9 g DPA and 2.2 g DHA	5.1 g	LA capsules	NSAID consumption during study and type of NSAIDs not reported	2	7
Remans et al. (2004)	4 months	Rheumatoid arthritis	55	1.4 g EPA, 211 mg DHA, 40 mg DPA, 16 mg ALA from liquid nutritional supplement	1.7 g	Water	Stable dose of prescribed NSAIDs during study; no differences in consumption between groups	4	12
Sundrarjun et al. (2004)	24 weeks	Rheumatoid arthritis	60	Four capsules of ω-3 PUFA, each providing 470 mg EPA and 370 mg DHA	3.4 g	Capsules (contents not reported)	Stable dose of NSAIDs during study; type of NSAIDs not reported	2	10
Adam et al. (2003)	8 months	Rheumatoid arthritis	68	One capsule per 10 kg body weight each containing 1 g menhaden oil providing 245.3 mg EPA/DHA (30 mg total/kg)	1.92 g[f]	Corn oil capsules	Prescribed NSAIDs were taken during study; decrease in NSAID consumption in treatment group	2	12
Sampalis et al. (2003)	3 months	Dysmenorrhea	70	Two 1g soft capsules of Neptune krill oil (NKO) daily during the first month, 8 days prior to and 2 days during menstruation	Content of ω-3 PUFA in NKO was not reported	Fish oil capsules	NSAIDs and acetaminophen were taken during study; type of NSAIDs not reported; decrease in NSAID consumption in treatment group	5	14
Nordstrom et al. (1995)	3 months	Rheumatoid arthritis	22	Thirty grams of flaxseed oil containing 32% ALA	9.6 g	LA capsules	Stable dose of NSAIDs during study; type of NSAIDs not reported	3	11
Geusens et al. (1994)	12 months	Rheumatoid arthritis	90	Six 1 g capsules of fish oil containing 42.5% ω-3 PUFA including 28% EPA and 6% DHA	2.6 g	Olive oil capsules	NSAIDs were taken during study; type of NSAIDs not reported; decrease in NSAID consumption in treatment group	3	10
Lau et al. (1993)	15 months	Rheumatoid arthritis	64	Ten fish oil capsules, each providing 171 mg EPA and 114 mg DHA	2.9 g	Air-filled capsules	NSAIDs were taken during study; type of NSAIDs not reported; decrease in NSAID consumption in treatment group	4	13

Table 1 (continued)

Study	Duration[a]	Patient population	n[b]	ω-3 PUFA supplement in treatment group[c]	Total ω-3 PUFA supplement in treatment group[c]	Type of placebo	Type of NSAID consumption	Quality score[d]	Validity score[e]
Nielsen et al. (1992)	12 weeks	Rheumatoid arthritis	57	Six capsules of fish oil, providing a total of 2.0 g EPA and 1.2 g DHA	3.2 g	Typical dietary FA capsules	Stable dose of NSAIDs during study; type of NSAIDs not reported	4	14
Skoldstam et al. (1992)	6 months	Rheumatoid arthritis	46	Ten capsules, each containing 1 g fish oil with 18% EPA and 12% DHA	3.0 g	Maize/olive/peppermint oil capsules	Prescribed NSAIDs were taken during study; decrease in NSAID consumption in treatment group	4	14
Kremer et al. (1990)	24 weeks	Rheumatoid arthritis	49	Fish oil capsules providing 54 mg/kg EPA and 36 mg/kg DHA	Not reported	Olive oil capsules	Stable dose of prescribed NSAIDs during study; patients reporting changes in NSAIDs were withdrawn	3	9
Tulleken et al. (1990)	3 months	Rheumatoid arthritis	28	Twelve fish oil capsules totaling 2.04 g EPA and 1.32 g DHA	3.4 g	Coconut oil capsules	No differences between groups in NSAID consumption at start of study; NSAID consumption during study and type of NSAIDs not reported	4	13
van der Tempel et al. (1990)	36 weeks	Rheumatoid arthritis	16	Twelve fish oil capsules providing a total of 2.04 g EPA and 1.32 g DHA	3.4 g	Coconut oil capsules	NSAID consumption during study and type of NSAIDs not reported	4	12
Cleland et al. (1988)	12 weeks	Rheumatoid arthritis	60	Eighteen 1.0 g capsules of fish oil providing 3.2 g EPA and 2.0 g DHA	5.2 g	Olive oil capsules	Stable dose of NSAIDs during study; type of NSAIDs not reported	4	10
Magaro et al. (1988)	1 month	Rheumatoid arthritis	12	Nine capsules of fish oil providing a total of 1.6 g EPA and 1.1 g DHA	2.7 g	Diet high in saturated FA	Stable dose of NSAIDs during study; type of NSAIDs not reported	1	5
Kremer et al. (1985)	12 weeks	Rheumatoid arthritis	52	Ten capsules providing a total of 1.8 g EPA per day	1.8 g	Paraffin wax-filled capsules	All patients on either aspirin or NSAIDs; consumption during study and type of NSAIDs not reported	3	12

Abbreviations: ALA, α-linolenic acid; DHA, docosahexaenoic acid; DPA, docosapentaenoic acid; EPA, eicosapentaenoic acid; LA, linoleic acid.
[a] Based on the total duration of the study including follow-up assessments.
[b] Number of patients reported is based on the number of patients approached at the beginning of the study and may be different from the number patients in analysis.
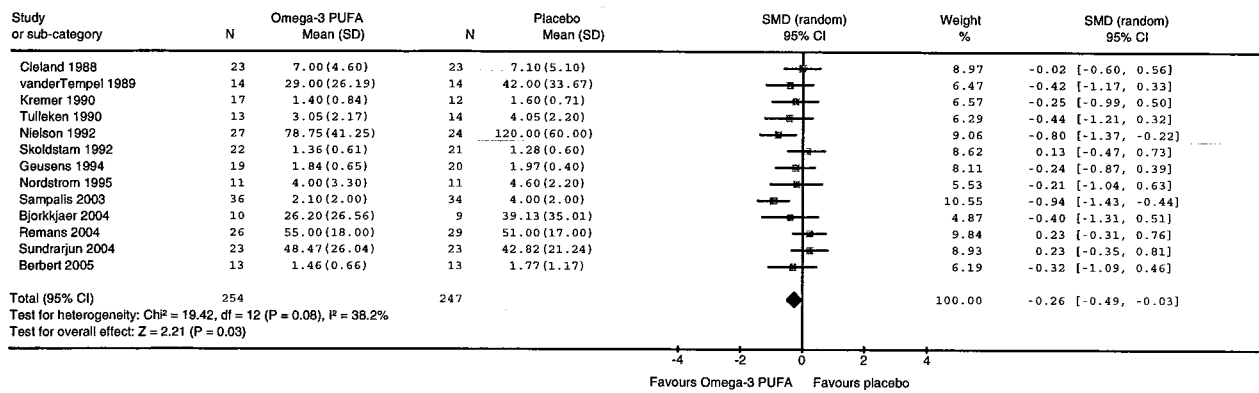[c] Based on daily intake.
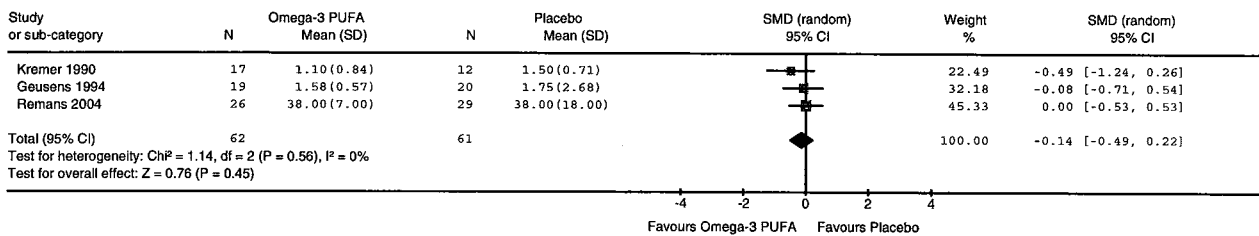[d] Assessed based on the Jadad et al. (1996) scale.
[e] Assessed based on the Oxford Pain Validity Scale (OPVS) scale by two independent reviewers blinded to authors, institutions, addresses, acknowledgements and publication details of each article.
[f] Based on a reported mean body weight of 69.3 kg.

Study or sub-category	Omega-3 PUFA N	Omega-3 PUFA Mean (SD)	Placebo N	Placebo Mean (SD)	SMD (random) 95% CI	Weight %	SMD (random) 95% CI
Cleland 1988	23	7.00(4.60)	23	7.10(5.10)		8.97	-0.02 [-0.60, 0.56]
vanderTempel 1989	14	29.00(26.19)	14	42.00(33.67)		6.47	-0.42 [-1.17, 0.33]
Kremer 1990	17	1.40(0.84)	12	1.60(0.71)		6.57	-0.25 [-0.99, 0.50]
Tulleken 1990	13	3.05(2.17)	14	4.05(2.20)		6.29	-0.44 [-1.21, 0.32]
Nielson 1992	27	78.75(41.25)	24	120.00(60.00)		9.06	-0.80 [-1.37, -0.22]
Skoldstam 1992	22	1.36(0.61)	21	1.28(0.60)		8.62	0.13 [-0.47, 0.73]
Geusens 1994	19	1.84(0.65)	20	1.97(0.40)		8.11	-0.24 [-0.87, 0.39]
Nordstrom 1995	11	4.00(3.30)	11	4.60(2.20)		5.53	-0.21 [-1.04, 0.63]
Sampalis 2003	36	2.10(2.00)	34	4.00(2.00)		10.55	-0.94 [-1.43, -0.44]
Bjorkkjaer 2004	10	26.20(26.56)	9	39.13(35.01)		4.87	-0.40 [-1.31, 0.51]
Remans 2004	26	55.00(18.00)	29	51.00(17.00)		9.84	0.23 [-0.31, 0.76]
Sundrarjun 2004	23	48.47(26.04)	23	42.82(21.24)		8.93	0.23 [-0.35, 0.81]
Berbert 2005	13	1.46(0.66)	13	1.77(1.17)		6.19	-0.32 [-1.09, 0.46]
Total (95% CI)	254		247			100.00	-0.26 [-0.49, -0.03]

Test for heterogeneity: Chi² = 19.42, df = 12 (P = 0.08), I² = 38.2%
Test for overall effect: Z = 2.21 (P = 0.03)

-4 -2 0 2 4
Favours Omega-3 PUFA   Favours placebo

Study or sub-category	Omega-3 PUFA N	Omega-3 PUFA Mean (SD)	Placebo N	Placebo Mean (SD)	SMD (random) 95% CI	Weight %	SMD (random) 95% CI
Kremer 1990	17	1.10(0.84)	12	1.50(0.71)		22.49	-0.49 [-1.24, 0.26]
Geusens 1994	19	1.58(0.57)	20	1.75(2.68)		32.18	-0.08 [-0.71, 0.54]
Remans 2004	26	38.00(7.00)	29	38.00(18.00)		45.33	0.00 [-0.53, 0.53]
Total (95% CI)	62		61			100.00	-0.14 [-0.49, 0.22]

Test for heterogeneity: Chi² = 1.14, df = 2 (P = 0.56), I² = 0%
Test for overall effect: Z = 0.76 (P = 0.45)

-4 -2 0 2 4
Favours Omega-3 PUFA   Favours Placebo

Study or sub-category	Omega-3 PUFA N	Omega-3 PUFA Mean (SD)	Placebo N	Placebo Mean (SD)	SMD (random) 95% CI	Weight %	SMD (random) 95% CI
Kremer 1985	23	56.00(48.00)	21	131.00(142.00)		13.78	-0.71 [-1.32, -0.10]
Cleland 1988	23	25.00(30.00)	23	38.00(45.00)		14.63	-0.33 [-0.92, 0.25]
vanderTempel 1989	14	15.00(18.70)	14	50.00(48.64)		9.83	-0.92 [-1.71, -0.14]
Kremer 1990	17	39.10(75.30)	12	26.30(32.70)		10.68	0.20 [-0.54, 0.94]
Tulleken 1990	13	45.00(35.70)	14	75.00(52.68)		9.98	-0.64 [-1.42, 0.14]
Nielson 1992	27	78.75(41.25)	24	120.00(60.00)		14.91	-0.80 [-1.37, -0.22]
Remans 2004	26	76.00(70.00)	29	71.00(40.00)		16.31	0.09 [-0.44, 0.62]
Berbert 2005	13	21.00(49.00)	13	46.00(47.00)		9.88	-0.50 [-1.29, 0.28]
Total (95% CI)	156		150			100.00	-0.43 [-0.72, -0.15]

Test for heterogeneity: Chi² = 10.77, df = 7 (P = 0.15), I² = 35.0%
Test for overall effect: Z = 2.95 (P = 0.003)

-4 -2 0 2 4
Favours Omega-3 PUFA   Favours Placebo

Study or sub-category	Omega-3 PUFA N	Omega-3 PUFA Mean (SD)	Placebo N	Placebo Mean (SD)	SMD (random) 95% CI	Weight %	SMD (random) 95% CI
Kremer 1985	23	6.40(5.60)	21	9.00(8.30)		10.40	-0.36 [-0.96, 0.23]
Cleland 1988	23	9.50(7.50)	23	12.00(10.25)		10.98	-0.27 [-0.85, 0.31]
vanderTempel 1989	14	29.00(26.19)	14	42.00(33.67)		6.58	-0.42 [-1.17, 0.33]
Kremer 1990	17	3.00(5.15)	12	6.20(4.15)		6.40	-0.65 [-1.41, 0.11]
Tulleken 1990	13	14.50(12.69)	14	16.50(8.78)		6.47	-0.18 [-0.94, 0.58]
Nielson 1992	27	8.00(3.00)	24	11.00(5.00)		11.44	-0.73 [-1.30, -0.16]
Geusens 1994	19	15.00(8.72)	20	19.00(13.42)		9.25	-0.34 [-0.98, 0.29]
Adam 2003	30	33.60(18.07)	30	36.00(21.91)		14.44	-0.12 [-0.62, 0.39]
Remans 2004	26	10.70(4.10)	29	9.70(5.10)		13.14	0.21 [-0.32, 0.74]
Sundrarjun 2004	23	9.13(6.62)	23	12.30(10.31)		10.90	-0.36 [-0.94, 0.22]
Total (95% CI)	215		210			100.00	-0.29 [-0.48, -0.10]

Test for heterogeneity: Chi² = 7.35, df = 9 (P = 0.60), I² = 0%
Test for overall effect: Z = 2.97 (P = 0.003)

-4 -2 0 2 4
Favours Omega-3 PUFA   Favours placebo

Fig. 3. Analysis of data used in overall result assessment from studies providing 3–4 month supplementation of ω-3 PUFAs. Conducted using Cochrane Review Manager 4.2.8. software. SD, standard deviation; SMD, standardized mean difference; CI, confidence interval.

showed significant improvements. Improvements in morning stiffness and NSAID consumption were noted, though this result did not reach significance (SMD: − 0.72; 95% CI: −1.70 to 0.25, p = 0.15 for morning stiffness, and SMD: −0.65; 95% CI: −1.40 to 0.09, p = 0.09 for NSAID consumption). Significant effects were not found for patient assessed pain and Ritchie articular index. Of the six studies reporting outcomes
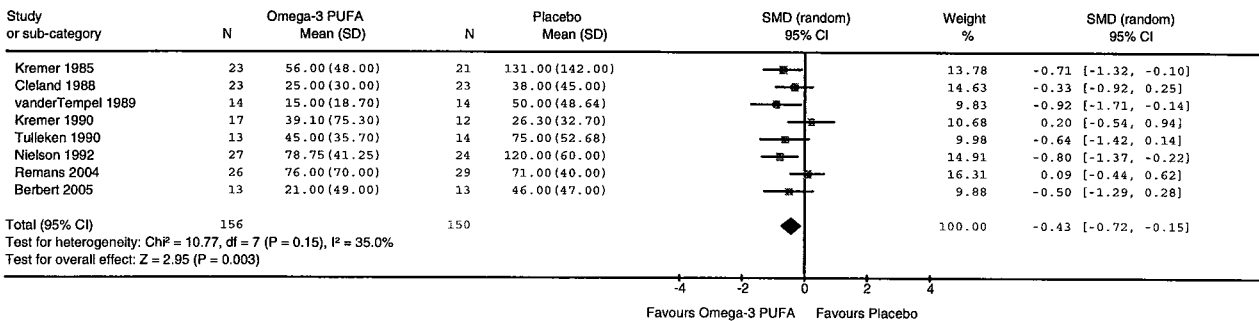
Review: Omega-3 polyunsaturated fatty acids for pain
Comparison: 02 Omega-3 polyunsaturated fatty acids versus placebo for joint pain: supplementation for 3-4 months
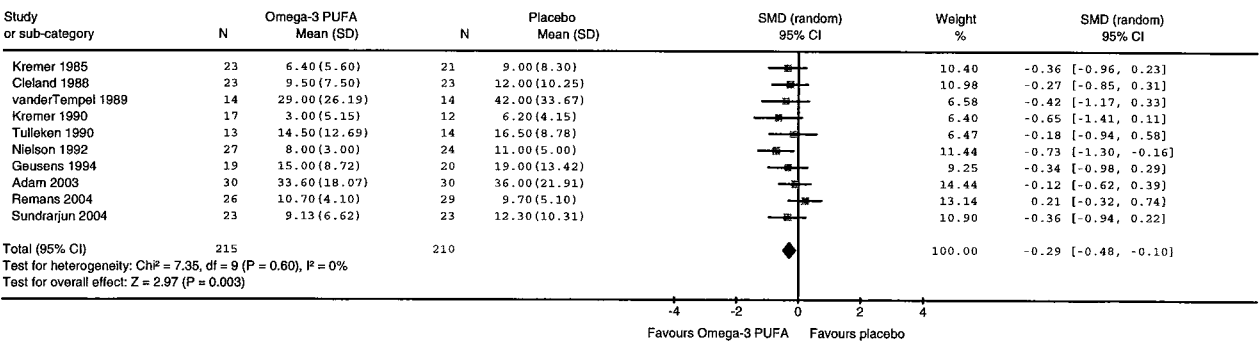Outcome: 05 Ritchie Articular Index

Study or sub-category	Omega-3 PUFA N	Omega-3 PUFA Mean (SD)	Placebo N	Placebo Mean (SD)	SMD (random) 95% CI	Weight %	SMD (random) 95% CI
Tulleken 1990	13	15.25(15.12)	14	14.00(7.36)		20.26	0.10 [-0.65, 0.86]
Skoldstam 1992	22	14.20(6.10)	21	11.50(5.04)		31.37	0.47 [-0.13, 1.08]
Geusens 1994	19	19.80(17.44)	20	24.60(17.89)		29.04	-0.27 [-0.90, 0.36]
Berbert 2005	13	7.60(6.70)	13	5.50(7.50)		19.33	0.29 [-0.49, 1.06]
Total (95% CI)	67		68			100.00	0.15 [-0.19, 0.49]

Test for heterogeneity: Chi² = 2.89, df = 3 (P = 0.41), I² = 0%
Test for overall effect: Z = 0.85 (P = 0.40)

-4 -2 0 2 4
Favours Omega-3 PUFA   Favours Placebo

Review: Omega-3 polyunsaturated fatty acids for pain
Comparison: 02 Omega-3 polyunsaturated fatty acids versus placebo for joint pain: supplementation for 3-4 months
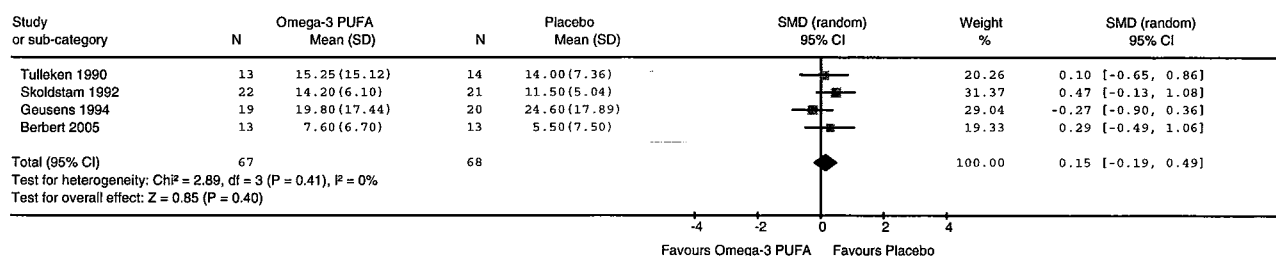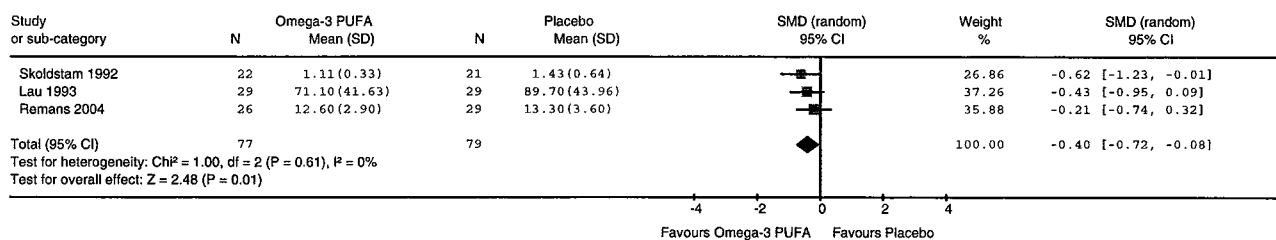Outcome: 06 NSAID consumption

Study or sub-category	Omega-3 PUFA N	Omega-3 PUFA Mean (SD)	Placebo N	Placebo Mean (SD)	SMD (random) 95% CI	Weight %	SMD (random) 95% CI
Skoldstam 1992	22	1.11(0.33)	21	1.43(0.64)		26.86	-0.62 [-1.23, -0.01]
Lau 1993	29	71.10(41.63)	29	89.70(43.96)		37.26	-0.43 [-0.95, 0.09]
Remans 2004	26	12.60(2.90)	29	13.30(3.60)		35.88	-0.21 [-0.74, 0.32]
Total (95% CI)	77		79			100.00	-0.40 [-0.72, -0.08]

Test for heterogeneity: Chi² = 1.00, df = 2 (P = 0.61), I² = 0%
Test for overall effect: Z = 2.48 (P = 0.01)

-4 -2 0 2 4
Favours Omega-3 PUFA   Favours Placebo

Fig. 3 (*continued*)

at two months or less (Fig. 5), significant effects were not found in any pain outcome measures. Improvement in Ritchie articular index was observed at two months or less (SMD: −1.22; 95% CI: −2.50 to 0.06, $p = 0.06$); however, this result is based on a small sample size ($n = 6$) from only one study.

3.2.2. Subgroup analyses
3.2.2.1. High-dose versus low-dose supplementation.
Subgroup analyses were conducted based on the dose of ω-3 PUFAs as well as type of placebo (olive oil or non-olive oil). Studies that provided high-dose ω-3 PUFAs (i.e., >2.7 g/day of EPA and DHA) showed greater improvements in morning stiffness (SMD: −0.50; 95% CI: −0.81 to −0.19, $p = 0.001$), and number of painful and/or tender joints (SMD: −0.46; 95% CI: −0.76 to −0.17, $p = 0.002$) compared to low-dose ω-3 PUFAs (SMD: −0.30; 95% CI: −1.07 to 0.48, $p = 0.46$ for morning stiffness, SMD: −0.12; 95% CI: −0.40 to 0.16, $p = 0.38$ for number of painful and/or tender joints). Although patient assessed pain was significant for high-dose, but not low-dose ω-3 PUFAs, the effect sizes were comparable (SMD: −0.22; 95% CI: −0.44 to 0.00, $p = 0.05$ for high-dose, and SMD: −0.32; 95% CI: −1.04 to 0.39, $p = 0.37$ for low-dose) raising the possibility of insufficient power for the low-dose effect size.

3.2.2.2. Olive oil versus non-olive oil placebo.
Studies employing a non-olive oil placebo showed greater improvements for patient assessed pain (SMD: −0.43; 95% CI: −0.74 to −0.12, $p = 0.007$) and morning stiffness (SMD: −0.54; 95% CI: −0.87 to −0.21, $p = 0.001$) relative to studies employing an olive oil placebo (SMD: −0.07; 95% CI: −0.39 to 0.24, $p = 0.65$ for patient assessed pain, and SMD: −0.12; 95% CI: −0.63 to 0.40, $p = 0.66$ for morning stiffness). There was little difference in painful and/or tender joint count between olive oil-controlled studies (SMD: −0.39; 95% CI: −0.76 to −0.02, $p = 0.04$) and non-olive oil-controlled studies (SMD: 0.25; 95% CI: −0.52 to 0.03, $p = 0.08$), as both showed favourable results. One study was excluded from this analysis since the type of placebo administered was not reported (Sundrarjun et al., 2004).

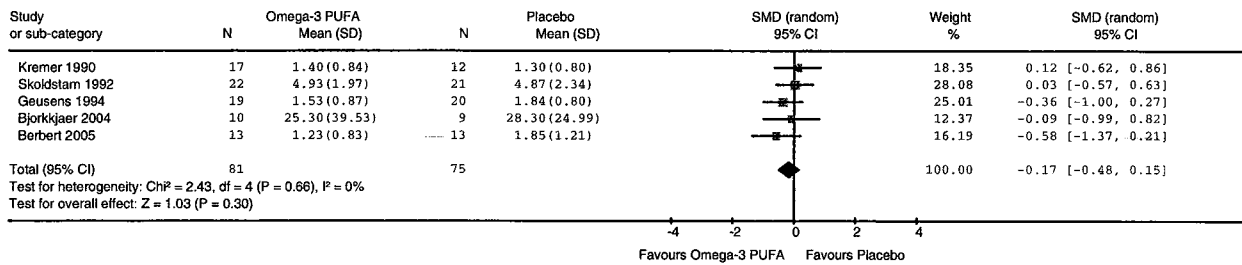### 3.3. Methodological quality and validity

The Jadad et al. (1996) quality index scores of the 17 articles ranged from one to five with a mean ± SD of 3.1 ± 1.1. Twelve of these trials received three or more points, and five trials received two or fewer points. Among the seven studies excluded from analysis, scores ranged from one to four with a mean ± SD of 3.0 ± 1.2. Five of these trials received three or more points, and two received two or fewer points. The mean quality score of the included versus excluded articles did not differ significantly ($t(22) = 0.24$, $p = 0.81$).

We sought to determine how exclusion of poor quality trials scoring two points or less on the Jadad et al. (1996) scale would affect the results. Exclusion of these trials had no material effect on the outcomes of the main analysis (p values that were (non) significant with all trials included remained so when poor quality trials were excluded).
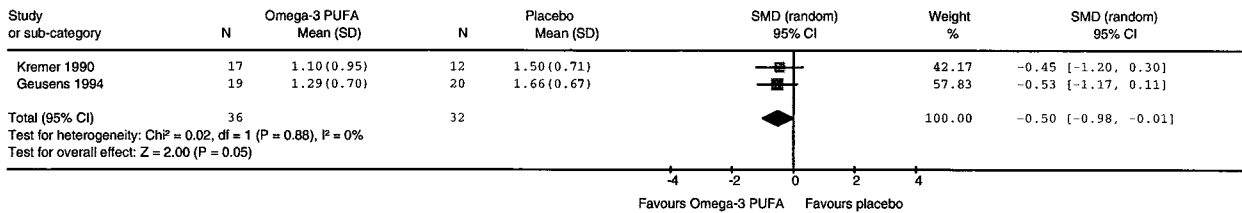
The Oxford Pain Validity Scale scores (Smith et al., 2000) of the 17 articles included in analysis ranged from five to 14 with a mean ± SD of 10.8 ± 2.9. Among the seven studies excluded from analysis, scores ranged from five to 12, with a mean ± SD of 9.4 ± 2.3. The

Review: Omega-3 polyunsaturated fatty acids for pain
Comparison: 03 Omega-3 polyunsaturated fatty acids versus placebo for joint pain: supplementation for 5 months or longer
Outcome: 01 Patient Assessment of Pain

Study or sub-category	N	Omega-3 PUFA Mean (SD)	N	Placebo Mean (SD)	SMD (random) 95% CI	Weight %	SMD (random) 95% CI
Kremer 1990	17	1.40(0.84)	12	1.30(0.80)		18.35	0.12 [-0.62, 0.86]
Skoldstam 1992	22	4.93(1.97)	21	4.87(2.34)		28.08	0.03 [-0.57, 0.63]
Geusens 1994	19	1.53(0.87)	20	1.84(0.80)		25.01	-0.36 [-1.00, 0.27]
Bjorkkjaer 2004	10	25.30(39.53)	9	28.30(24.99)		12.37	-0.09 [-0.99, 0.82]
Berbert 2005	13	1.23(0.83)	13	1.85(1.21)		16.19	-0.58 [-1.37, 0.21]
Total (95% CI)	81		75			100.00	-0.17 [-0.48, 0.15]

Test for heterogeneity: Chi² = 2.43, df = 4 (P = 0.66), I² = 0%
Test for overall effect: Z = 1.03 (P = 0.30)

-4 -2 0 2 4
Favours Omega-3 PUFA   Favours Placebo

Review: Omega-3 polyunsaturated fatty acids for pain
Comparison: 03 Omega-3 polyunsaturated fatty acids versus placebo for joint pain: supplementation for 5 months or longer
Outcome: 02 Physician's Assessment of Pain

Study or sub-category	N	Omega-3 PUFA Mean (SD)	N	Placebo Mean (SD)	SMD (random) 95% CI	Weight %	SMD (random) 95% CI
Kremer 1990	17	1.10(0.95)	12	1.50(0.71)		42.17	-0.45 [-1.20, 0.30]
Geusens 1994	19	1.29(0.70)	20	1.66(0.67)		57.83	-0.53 [-1.17, 0.11]
Total (95% CI)	36		32			100.00	-0.50 [-0.98, -0.01]

Test for heterogeneity: Chi² = 0.02, df = 1 (P = 0.88), I² = 0%
Test for overall effect: Z = 2.00 (P = 0.05)

-4 -2 0 2 4
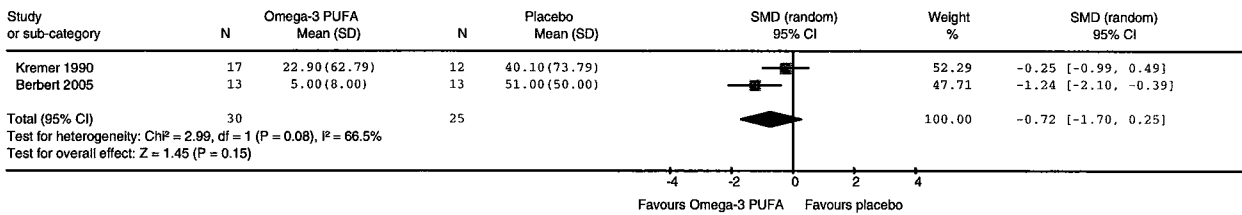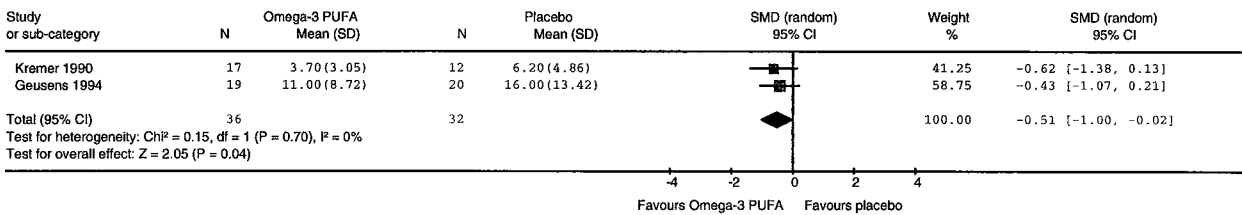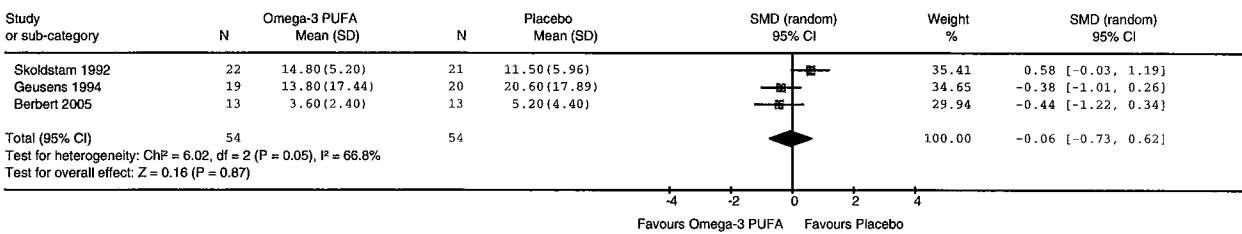Favours Omega-3 PUFA   Favours placebo

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Review: Omega-3 polyunsaturated fatty acids for pain
Comparison: 03 Omega-3 polyunsaturated fatty acids versus placebo for joint pain: supplementation for 5 months or longer
Outcome: 03 Morning Stiffness (minutes)

Study or sub-category	N	Omega-3 PUFA Mean (SD)	N	Placebo Mean (SD)	SMD (random) 95% CI	Weight %	SMD (random) 95% CI
Kremer 1990	17	22.90(62.79)	12	40.10(73.79)		52.29	-0.25 [-0.99, 0.49]
Berbert 2005	13	5.00(8.00)	13	51.00(50.00)		47.71	-1.24 [-2.10, -0.39]
Total (95% CI)	30		25			100.00	-0.72 [-1.70, 0.25]

Test for heterogeneity: Chi² = 2.99, df = 1 (P = 0.08), I² = 66.5%
Test for overall effect: Z = 1.45 (P = 0.15)

-4 -2 0 2 4
Favours Omega-3 PUFA   Favours placebo

Review: Omega-3 polyunsaturated fatty acids for pain
Comparison: 03 Omega-3 polyunsaturated fatty acids versus placebo for joint pain: supplementation for 5 months or longer
Outcome: 04 Number of Painful / Tender Joints

Study or sub-category	N	Omega-3 PUFA Mean (SD)	N	Placebo Mean (SD)	SMD (random) 95% CI	Weight %	SMD (random) 95% CI
Kremer 1990	17	3.70(3.05)	12	6.20(4.86)		41.25	-0.62 [-1.38, 0.13]
Geusens 1994	19	11.00(8.72)	20	16.00(13.42)		58.75	-0.43 [-1.07, 0.21]
Total (95% CI)	36		32			100.00	-0.51 [-1.00, -0.02]

Test for heterogeneity: Chi² = 0.15, df = 1 (P = 0.70), I² = 0%
Test for overall effect: Z = 2.05 (P = 0.04)

-4 -2 0 2 4
Favours Omega-3 PUFA   Favours placebo

Review: Omega-3 polyunsaturated fatty acids for pain
Comparison: 03 Omega-3 polyunsaturated fatty acids versus placebo for joint pain: supplementation for 5 months or longer
Outcome: 05 Ritchie Articular Index

Study or sub-category	N	Omega-3 PUFA Mean (SD)	N	Placebo Mean (SD)	SMD (random) 95% CI	Weight %	SMD (random) 95% CI
Skoldstam 1992	22	14.80(5.20)	21	11.50(5.96)		35.41	0.58 [-0.03, 1.19]
Geusens 1994	19	13.80(17.44)	20	20.60(17.89)		34.65	-0.38 [-1.01, 0.26]
Berbert 2005	13	3.60(2.40)	13	5.20(4.40)		29.94	-0.44 [-1.22, 0.34]
Total (95% CI)	54		54			100.00	-0.06 [-0.73, 0.62]

Test for heterogeneity: Chi² = 6.02, df = 2 (P = 0.05), I² = 66.8%
Test for overall effect: Z = 0.16 (P = 0.87)

-4 -2 0 2 4
Favours Omega-3 PUFA   Favours Placebo

Review: Omega-3 polyunsaturated fatty acids for pain
Comparison: 03 Omega-3 polyunsaturated fatty acids versus placebo for joint pain: supplementation for 5 months or longer
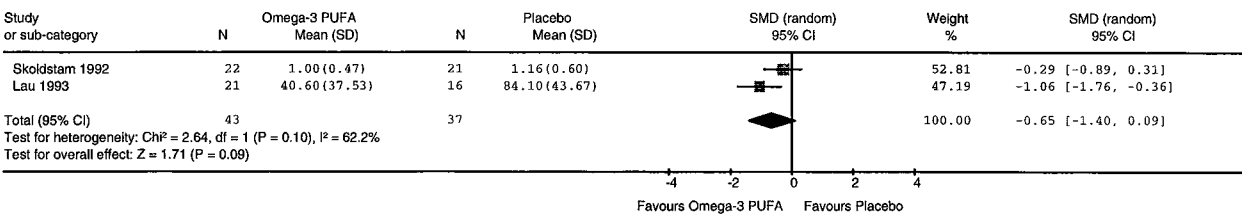**Outcome:** 06 NSAID consumption (defined daily doses)

Study or sub-category	N	Omega-3 PUFA Mean (SD)	N	Placebo Mean (SD)	SMD (random) 95% CI	Weight %	SMD (random) 95% CI
Skoldstam 1992	22	1.00(0.47)	21	1.16(0.60)		52.81	-0.29 [-0.89, 0.31]
Lau 1993	21	40.60(37.53)	16	84.10(43.67)		47.19	-1.06 [-1.76, -0.36]
Total (95% CI)	43		37			100.00	-0.65 [-1.40, 0.09]

Test for heterogeneity: Chi² = 2.64, df = 1 (P = 0.10), I² = 62.2%
Test for overall effect: Z = 1.71 (P = 0.09)

-4 -2 0 2 4
Favours Omega-3 PUFA   Favours Placebo

Fig. 4. Analysis of data used in overall result assessment from studies providing supplementation of ω-3 PUFA for longer than 5 months. Conducted using Cochrane Review Manager 4.2.8. software. SD, standard deviation; SMD, standardized mean difference; CI, confidence interval.
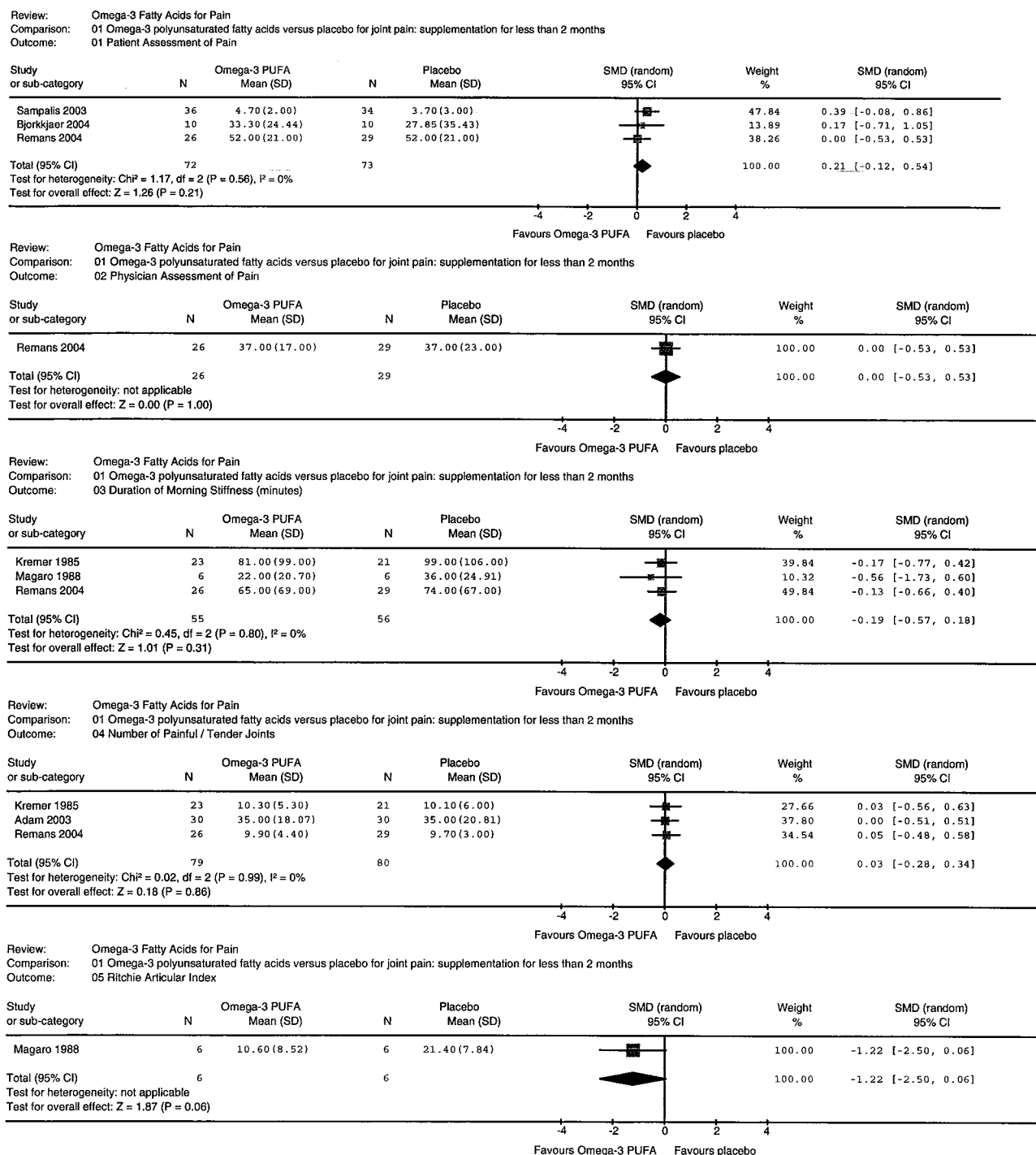
Study or sub-category	Omega-3 PUFA N	Mean (SD)	Placebo N	Mean (SD)	SMD (random) 95% CI	Weight %	SMD (random) 95% CI
Sampalis 2003	36	4.70(2.00)	34	3.70(3.00)		47.84	0.39 [-0.08, 0.86]
Bjorkkjaer 2004	10	33.30(24.44)	10	27.85(35.43)		13.89	0.17 [-0.71, 1.05]
Remans 2004	26	52.00(21.00)	29	52.00(21.00)		38.26	0.00 [-0.53, 0.53]
Total (95% CI)	72		73			100.00	0.21 [-0.12, 0.54]

Test for heterogeneity: Chi² = 1.17, df = 2 (P = 0.56), I² = 0%
Test for overall effect: Z = 1.26 (P = 0.21)

-4 -2 0 2 4
Favours Omega-3 PUFA   Favours placebo

Study or sub-category	Omega-3 PUFA N	Mean (SD)	Placebo N	Mean (SD)	SMD (random) 95% CI	Weight %	SMD (random) 95% CI
Remans 2004	26	37.00(17.00)	29	37.00(23.00)		100.00	0.00 [-0.53, 0.53]
Total (95% CI)	26		29			100.00	0.00 [-0.53, 0.53]

Test for heterogeneity: not applicable
Test for overall effect: Z = 0.00 (P = 1.00)

-4 -2 0 2 4
Favours Omega-3 PUFA   Favours placebo

Study or sub-category	Omega-3 PUFA N	Mean (SD)	Placebo N	Mean (SD)	SMD (random) 95% CI	Weight %	SMD (random) 95% CI
Kremer 1985	23	81.00(99.00)	21	99.00(106.00)		39.84	-0.17 [-0.77, 0.42]
Magaro 1988	6	22.00(20.70)	6	36.00(24.91)		10.32	-0.56 [-1.73, 0.60]
Remans 2004	26	65.00(69.00)	29	74.00(67.00)		49.84	-0.13 [-0.66, 0.40]
Total (95% CI)	55		56			100.00	-0.19 [-0.57, 0.18]

Test for heterogeneity: Chi² = 0.45, df = 2 (P = 0.80), I² = 0%
Test for overall effect: Z = 1.01 (P = 0.31)

-4 -2 0 2 4
Favours Omega-3 PUFA   Favours placebo

Study or sub-category	Omega-3 PUFA N	Mean (SD)	Placebo N	Mean (SD)	SMD (random) 95% CI	Weight %	SMD (random) 95% CI
Kremer 1985	23	10.30(5.30)	21	10.10(6.00)		27.66	0.03 [-0.56, 0.63]
Adam 2003	30	35.00(18.07)	30	35.00(20.81)		37.80	0.00 [-0.51, 0.51]
Remans 2004	26	9.90(4.40)	29	9.70(3.00)		34.54	0.05 [-0.48, 0.58]
Total (95% CI)	79		80			100.00	0.03 [-0.28, 0.34]

Test for heterogeneity: Chi² = 0.02, df = 2 (P = 0.99), I² = 0%
Test for overall effect: Z = 0.18 (P = 0.86)

-4 -2 0 2 4
Favours Omega-3 PUFA   Favours placebo

Study or sub-category	Omega-3 PUFA N	Mean (SD)	Placebo N	Mean (SD)	SMD (random) 95% CI	Weight %	SMD (random) 95% CI
Magaro 1988	6	10.60(8.52)	6	21.40(7.84)		100.00	-1.22 [-2.50, 0.06]
Total (95% CI)	6		6			100.00	-1.22 [-2.50, 0.06]

Test for heterogeneity: not applicable
Test for overall effect: Z = 1.87 (P = 0.06)

-4 -2 0 2 4
Favours Omega-3 PUFA   Favours placebo

Fig. 5. Analysis of data used in overall result assessment from studies providing less than two months supplementation of ω-3 PUFAs. Conducted using Cochrane Review Manager 4.2.8. software. SD, standard deviation; SMD, standardized mean difference; CI, confidence interval.

mean validity score of the included versus excluded articles did not differ significantly ($t(22) = 1.09$, $p = 0.29$).

4. Discussion

The results of the present meta-analysis support the hypothesis that ω-3 PUFA supplementation improves pain outcomes after three months, particularly with respect to patient assessed pain, duration of morning stiffness, number of painful and/or tender joints, and NSAID consumption.

Two previous meta-analyses of ω-3 PUFA supplementation for RA have been published. The first was conducted more than 10 years ago (Fortin et al., 1995) and found a modest effect of fish oil supplementation

on joint tenderness and morning stiffness after three months. The second meta-analysis (MacLean et al., 2004) did not detect any effect on patient assessed pain. In contrast to the present meta-analysis which focused on six pain-related outcomes, MacLean et al. (2004) focused on immune mediated diseases, bone metabolism, and gastrointestinal/renal diseases. Our results differ from the previous meta-analyses in showing a stronger effect than that reported by Fortin et al. (1995) and a beneficial effect compared to the lack of effect for patient assessed pain by MacLean et al. (2004). Reasons for the discrepancy between the results of the present meta-analysis and the earlier ones include the fact that Fortin et al. (1995) did not include measures of patient assessed pain, physician assessed pain, Ritchie articular index, or NSAID consumption, and MacLean et al. (2004) only addressed patient assessed pain and NSAID consumption. Furthermore, we reported on eight additional trials that were either not included by Fortin et al. (1995) and MacLean et al. (2004) or were published subsequently. We also included one study measuring joint pain in patients with dysmenorrhea (Sampalis et al., 2003) and one measuring rheumatic joint pain in patients with inflammatory bowel disease (Bjorkkjaer et al., 2004). Finally, we excluded one non-randomized trial (Kremer et al., 1987) that Fortin et al. (1995) included.

Notwithstanding the positive outcome of the present meta-analysis, a number of factors may have reduced the apparent efficacy of ω-3 PUFAs in the studies analyzed. (1) The use of a variety of doses and treatment periods in different studies limited the effect size detected. With the exception of two studies (Kremer et al., 1990; Adam et al., 2003), a dosage of ω-3 PUFAs relative to patient body weight was not provided. (2) Consideration of treatment time showed that a minimum of three months was required for a therapeutic effect, but there were only six studies available for the 6-month analysis, thus decreasing the power for this analysis. (3) It was previously suggested that a dose of 2.7 g/day of EPA and DHA is required to achieve anti-inflammatory effects (Stamp et al., 2005). One study indeed found that high-dose ω-3 PUFAs were more effective than a low-dose in reducing pain in RA (Geusens et al., 1994). In our analysis, 11 of the 16 studies at 3–4 months used a dose of EPA/DHA above 2.7 g ω-3 PUFAs per day. Significant improvements were noted in patient assessed pain and morning stiffness among studies providing high-dose but not low-dose ω-3 PUFA supplementation. (4) The use of additional analgesics and supplements likely further obscures the benefits of EPA/DHA supplementation but many studies did not provide these data. (5) Long-chain ω-3 PUFAs compete with other fatty acids for incorporation into phospholipids. Reducing the intake of ω-6 fatty acids (e.g., linoleic acid), which are metabolized to arachidonic acid and inflammatory eicosanoids, would be expected to increase the effectiveness of ω-3 PUFA supplements (Stamp et al., 2005). Indeed, a study of RA patients demonstrated greater efficacy of EPA/DHA when ω-6 PUFA consumption was decreased (Adam et al., 2003). Linoleic acid intake was not controlled in most of the studies analyzed. (6) Olive oil was used as the placebo in the control group in some of the studies (Cleland et al., 1988; Kremer et al., 1990; Skoldstam et al., 1992; Geusens et al., 1994), but olive oil itself may have anti-inflammatory properties, thereby lessening the relative effects of EPA/DHA when compared with (olive oil) placebo. The main constituent of olive oil, oleic acid, may compete with arachidonic acid for incorporation into phospholipids. Olive oil also contains phenols, such as tyrosol and β-sitosterol, which have anti-inflammatory actions (Moreno et al., 2001). (7) Finally, in most of the studies, it was not noted whether precautions were taken to prevent oxidation of EPA/DHA.

In order to maximize the therapeutic effects and improve the quality and validity of future trials, it is recommended that all studies report concomitant analgesics and doses since without these data it is difficult to assess the true magnitude of effect of ω-3 PUFA supplementation. In addition, we recommend use of high-dose ω-3 PUFAs (at least 2.7 g/day of EPA and DHA) for a minimum duration of 3 months using a non-olive oil placebo control condition.

Are EPA/DHA supplements useful for other types of chronic inflammatory pain? Many patients with osteoarthritis or chronic back pain might benefit from alternatives to NSAIDs, yet there are no controlled clinical trials at present. Inflammation was found to be more prominent in the early stages of osteoarthritis compared to the latter stages (Benito et al., 2005), suggesting the early stages might be more susceptible to EPA/DHA. Consistent with the prostaglandin dependent mechanism underlying dysmenorrhea, pain associated with the menstrual cycle was reduced by fish oil combined with vitamin B12 (Deutch et al., 2000) and by Neptune krill oil, which is enriched in ω-3 PUFAs (Sampalis et al., 2003).

The mechanisms by which ω-3 PUFAs reduce pain are not known. It remains to be determined empirically whether the ability of EPA/DHA to reduce pain is due to one or more of the following possibilities: suppression of the inflammation underlying RA or inflammatory bowel disease; direct effects on prostaglandins or possibly cytokines in the spinal cord dorsal horn. Evidence is equivocal for an EPA/DHA mediated reduction in cytokine secretion in humans. As reviewed by Calder (2006), some studies that supply high-dose EPA or DHA to healthy volunteers (e.g., Kelley et al., 1999) resulted in a suppression of TNF-α or IL-1β release by monocytes,

whereas a number of other studies (e.g., Kew et al., 2004) failed to detect any changes in cytokine release.

Chronic neuropathic pain consequent to physical or viral injury to sensory nerves is mediated in part by hyperexcitable dorsal horn neurons (Marchand et al., 2005; Takeda et al., 2005; Wieseler-Frank et al., 2005), but it is a less attractive target for EPA/DHA than is chronic inflammatory pain. There are important differences in the mechanisms to these two types of chronic pain. Animal models of chronic neuropathic pain induced by spinal root ligation or sciatic nerve constriction show that prostaglandins are required to initiate the process, but are not necessary for its maintenance; and NSAIDs have limited efficacy in chronic neuropathic pain (Broom et al., 2004; Takeda et al., 2005). Rather, a critical factor in neuropathic pain is the activation in the spinal cord of non-neural glial cells, microglia and astrocytes (Marchand et al., 2005; Wieseler-Frank et al., 2005). Activated glia are characterized by proliferation, hypertrophy, and increased production of proinflammatory cytokines, such as IL-1β, TNF-α, and interleukin-6 (IL-6). Inhibitors of IL-1β administered intrathecally can reduce neuropathic pain, while transgenic mice with absent IL-1 signalling fail to develop neuropathic pain (Sweitzer et al., 2001; Marchand et al., 2005; Honore et al., 2006; Wolf et al., 2006). Glial activation was observed in one rat study of inflammatory pain induced by complete-Freund's adjuvant, but not in other reports (Zhang et al., 2003; Raghavendra et al., 2004; Honore et al., 2006). In chronic neuropathic pain animal models, microglia also secrete brain-derived neurotrophic factor (BDNF). This inverts the polarity of currents activated by the neurotransmitter γ-amino butyric acid, thereby causing disinhibition of dorsal horn neurons (Coull et al., 2005). Of these mechanisms of neuropathic pain, the production of inflammatory cytokines might potentially be reduced by EPA/DHA, but as noted above this is unclear. One study examined the effect of feeding various plant oils to rats following partial sciatic nerve ligation (Perez et al., 2005). In that report, heat hyperalgesia correlated negatively with the amount of α-linolenic acid in the test diets, raising the possibility that ω-3 PUFAs may enhance neuropathic pain. Since α-linolenic acid is poorly converted to EPA and DHA (James et al., 2003), further experiments are needed to directly test the effects of EPA and DHA in a neuropathic pain model.

In summary, the results of the present meta-analysis, examining ω-3 PUFA supplementation in patients with rheumatoid arthritis or joint pain secondary to inflammatory bowel disease and dysmenorrhea, suggest that EPA/DHA supplementation reduces patient assessed joint pain intensity, morning stiffness, number of painful and/or tender joints, and NSAID consumption. Omega-3 PUFA supplementation is an attractive adjunctive treatment for joint pain. Further studies in humans are required to optimize the analgesic effects of EPA/DHA in patients with arthritis and other types of chronic inflammatory pain.

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