EXTENDED REPORT

# Fish oil in knee osteoarthritis: a randomised clinical trial of low dose versus high dose

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## ABSTRACT

**Objectives** To determine whether high-dose fish oil is superior to low-dose supplementation for symptomatic and structural outcomes in knee osteoarthritis (OA).

**Methods** A randomised, double-blind, multicentre trial enrolled 202 patients with knee OA and regular knee pain. They were randomised 1:1 to high-dose fish oil (4.5 g omega-3 fatty acids) 15 mL/day or (2) low-dose fish oil (blend of fish oil and sunola oil; ratio of 1:9, 0.45 g omega-3 fatty acids) 15 mL/day. The primary endpoints were Western Ontario and McMaster Universities Arthritis Index (WOMAC) pain score at 3, 6, 12 and 24 months, and change in cartilage volume at 24 months. Secondary outcomes included WOMAC function, quality of life, analgesic and non-steroidal anti-inflammatory drug use and bone marrow lesion score.

**Results** Although there was improvement in both groups, the low-dose fish oil group had greater improvement in WOMAC pain and function scores at 2 years compared with the high-dose group, whereas between-group differences at 1 year did not reach statistical significance. There was no difference between the two groups in cartilage volume loss at 2 years. For other secondary endpoints, there was no difference between the two groups at 2 years.

**Conclusions** In people with symptomatic knee OA, there was no additional benefit of a high-dose fish oil compared with low-dose fish oil. The combination comparator oil appeared to have better efficacy in reducing pain at 2 years, suggesting that this requires further investigation.

**Trial registration number** Australian New Zealand Clinical Trials Registry (ACTRN 12607000415404).

## INTRODUCTION

Osteoarthritis (OA) is a major cause of disability in older persons.[1] Current medical treatment is confined to symptom control with paracetamol and/or non-steroidal anti-inflammatory drugs (NSAIDs), as well as physical therapy and weight loss.[2] Although NSAIDs transiently reduce knee OA pain, due to the adverse effects, American College of Rheumatology (ACR) guidelines recommend intermittent use only.[2] A systematic review of fish oil use in rheumatoid arthritis (RA) reported decreased NSAID use with fish oil,[3] and a randomised controlled trial (RCT) of high-dose fish oil in recent-onset RA demonstrated a higher remission rate.[4] Synovial inflammation is associated with severity of pain in knee OA[5–7] and has been variably associated with cartilage loss.[7 8] Since synovitis and cartilage degradation are common to both RA and OA, it is possible that fish oil may be useful in OA.

Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), the main omega-3 fatty acids in fish oil, decrease synthesis of the cyclooxygenase omega-6 fatty acid metabolite, prostaglandin E2 also a target of NSAID action. EPA and DHA are also precursors of the E-resolvins and D-resolvins that suppress inflammatory cytokine production and act to resolve inflammation.[9] In vitro experiments and animal OA models suggest potential benefit of EPA/DHA in OA, although few studies have been undertaken.[10–13] In healthy adults, higher baseline dietary intake of monounsaturated fats and n-6 fatty acids has been associated with increased bone marrow lesions (BMLs) on MRI 10 years later, but no significant effect on cartilage volume.[14] Data from the MOST study (n=472) showed a negative association between total n-3 fatty acid levels and patellofemoral cartilage loss, but no association with synovitis or tibiofemoral cartilage loss.[15] Neither study included n-3 fatty acids supplementation.

Community use of omega-3 supplements is widespread. An Australian study of 260 000 people reported 32.6% had taken omega-3 supplements within the past four weeks with presence of OA being positively correlated with use.[16] However, most people are taking a low median daily dose of 1 mL of fish oil, which contains approximately 30% (0.3 g) EPA+DHA.[17] Studies in RA and other inflammatory diseases have indicated that the anti-inflammatory dose of fish oil requires delivery of ≥2.7 g of EPA+DHA daily,[10] requiring approximately 10 mL of standard fish oil per day. Therefore, most people who self-medicate with fish oil are generally taking much less than the anti-inflammatory dose.

The aim of this study was to compare the effects of an anti-inflammatory dose of fish oil with a lower dose of fish oil (not considered to be in the anti-inflammatory range), in a double-blind RCT of knee OA. The comparator of low-dose fish oil was chosen for masking of high-dose fish oil and to allow compliance with recommendations on EPA +DHA intake for cardiovascular prevention.[18] The study hypothesis was that high-dose fish oil would have superior efficacy to low-dose fish oil for symptomatic and structural outcomes in people with knee OA.

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## METHODS

### Study design

We undertook a double-blind, randomised trial. Participants were recruited from the community through general media advertising and rheumatology databases at three Australian centres (August 2007–September 2009). Further details of the study protocol are available in online supplementary file.

### Participants

Participants were >40 years with clinical knee OA defined using ACR criteria[19] and visual analogue scale knee pain score >20 mm (0–100 mm scale). Exclusion criteria included severe radiographic knee OA in index knee (grade 3 radiographic joint space narrowing using Osteoarthritis Research Society International atlas[20]), dementia or inability to give informed consent, pregnancy or lactation, planned knee replacement surgery, long-term use (≥6 months) of high-dose fish oil (equivalent to 15 mL of oil) and contraindications to MRI.

### Run-in, randomisation and masking

Prior to randomisation, a 4-week run-in period with similarly flavoured oil (citrus-flavoured sunola oil), 15 mL/day, was performed to exclude participants intolerant of liquid oil. Participants who tolerated oil during the run-in period were randomly allocated to one of two treatment arms: high-dose or low-dose fish oil, 15 mL per day. High-dose fish oil contained EPA 18% and DHA 12%, supplying 4.5 g EPA+DHA per day. The comparator oil was a blend of low-dose fish oil and high-oleic sunola oil in a ratio of 1:9, supplying 0.45 g EPA+DHA per day, equivalent to 1.5 standard 1 g fish oil capsule daily. Both oils were flavoured with citrus oils and provided in identical dark 500 mL bottles. The oils, blending, masking and bottling were provided by Melrose Health, Victoria, Australia. Study oil bottles were returned at each study visit and volume of unconsumed oil was measured to assess compliance. Participants were provided with paracetamol (500 mg) tablets with instructions that they could safely use up to 8/day.

The computer-generated random allocation sequence and subsequent allocation was performed centrally at one pharmacy with stratification for study site. Participants and staff involved in patient care and assessment of MRI remained blinded throughout the study.

### Outcome measures

Primary outcomes were knee-specific pain scales (Western Ontario and McMaster Universities Arthritis (WOMAC) index) at 3, 6, 12 and 24 months and change in cartilage volume on MRI at 24 months. Secondary outcome measures were WOMAC function, quality of life, analgesic and NSAID use, change in BML score and safety outcomes.

The WOMAC numerical rating scale (NRS) 3.1 index for knee pain and function, measured on a 10-point numerical scale,[21] and the Assessment of Quality of Life utility instrument, which has been validated in both the general population and patients with OA,[22] were measured 3 monthly. Analgesic use was measured using pill counts for paracetamol and daily diary for NSAIDs, using NSAID equivalence scores.[23]

MRIs of the study knee were performed at baseline and 2 years with 1.5 T whole-body MR unit using a commercial receive-only extremity coil. The MRI sequence was a T1-weighted, fat-suppressed, three-dimensional (3D) gradient recall acquisition in the steady state; flip angle 55°; repetition time 58 ms; echo time 12 ms; field of view 16 cm; 60 partitions; 512×192 matrix; one acquisition time 11 min, 56 s. Sagittal images were obtained at a partition thickness of 1.5 mm and an in-plane resolution of 0.31×0.83 mm (512×192 pixels).

Individual cartilage plate volumes (medial tibia, lateral tibia and patella) were isolated from the total volume by manually drawing disarticulation contours around the cartilage boundaries on a section-by-section basis. Data were then resampled by means of bilinear and cubic interpolation (area of 312 and 1.5 mm thickness, continuous sections) for the final 3D rendering. There was one trained reader, blinded to treatment allocation and clinical data, with coefficient of variation of 2.1–2.6%.[24]

BMLs were assessed on a proton density-weighted fat saturation 2D fast spin echo sequence in the sagittal plane. They were defined as areas of increased signal adjacent to the subcortical bone at the medial tibial, medial femoral, lateral tibial, lateral femoral, superior patella and inferior patella sites. BMLs were scored by measuring the maximum area of the lesion ($mm^2$) at baseline and follow-up.[25] There was one trained reader, blinded to treatment allocation and clinical data, with intraclass correlation coefficient of 0.97.[25] BML size at all six sites was summed to create total BML size at each time point. A meaningful BML change was considered to be 140 $mm^2$ change in either direction, which corresponds to a one-unit change in WOMAC pain score.[25 26]

MRI scans at both baseline and end of study were available for cartilage reading (n=116), and BML reading (n=110) as only participants with readable scans at baseline and 24 months were included. All participants from one site were excluded from MRI analysis due to inconsistent MRI sequencing from baseline to 24 months (n=51). Further participants were excluded due to loss to follow-up, non-readable MRI, screws in the knee, incorrect sequence at one time point or incorrect knee scanned at one time point.

### Serum fatty acid analysis

Fasting serum phospholipid fatty acid from two sites (Adelaide and Sydney; n=150) were measured at each clinic visit by capillary gas chromatography.[27]

### Sample size

Sample sizes of 100 per treatment group were selected based on power calculations for longitudinal data with six treatment visits, $\alpha=0.05$, $\beta=0.2$, an attrition rate of 5% per visit and a standardised treatment effect at the end of the study of 0.4 (ie, a medium effect).

### Statistical analysis

Primary hypotheses were tested using intention-to-treat (ITT) analysis, with secondary per protocol (PP) analysis of those who finished the 24-month visit taking study oil.

Analysis of outcomes at each visit was performed by constrained longitudinal data analysis,[28] using R statistical software.[29] Mixed effects models were estimated, with both patient and centre as random effects, and an autocorrelation error structure using the nlme library.[30] WOMAC scores were analysed from 20 multiply imputed data sets, imputed using the Amelia library.[31] Treatment effects for normally distributed variables were expressed as mean differences. Non-normally distributed variables were log-transformed as appropriate, and treatment effects for these variables were expressed as ratios. Relative risks were estimated for dichotomous outcomes. Causal mediation analysis, for the influence of weight gain on WOMAC outcomes, was performed using the R library mediation.[32]



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## RESULTS

### Participants

A total of 351 participants were screened (figure 1). A further 49 participants failed to complete the run-in period. Two-hundred and two participants were randomised to either arm. There was one protocol violation following randomisation. Although 54 (26.7%) discontinued the intervention, follow-up was 84% at 24 months as consenting participants were evaluated at 12 and 24 months irrespective of continuing the intervention. At baseline, participants in each group were well-matched, except for gender (table 1). There were more female participants randomised to the high-dose fish oil group (59%) compared with low-dose fish oil group (40%, p<0.01). The majority had evidence of radiographic OA (194/202; 96%).

Withdrawal from therapy was higher in the high-dose compared with the low-dose group (35% vs 20%) and occurred earlier (median time to cessation 3 vs 7.5 months). Reasons for withdrawals are shown in figure 1.

### Pain and function

The low-dose fish oil group had lower pain scores at 18 and 24 months and better functional limitation scores at 24 months compared with the high-dose group (figure 2D, E and table 2). These differences were demonstrated in both ITT and PP analyses (table 2). Adjustment for gender had little or no effect on the outcomes (table 2).

There was no difference between the two groups in the use of paracetamol or NSAIDs (see online supplementary table S1, figure S1 and supplementary data) during the study, nor any difference in quality of at any time point (figure 2F).

### MRI results

There was no statistically significant change in total cartilage volume from baseline to 24 months and no difference between the groups in the changes over 24 months (table 3). There was no difference in the proportion of participants who had a clinically significant change in BML over 24 months (table 3).

### Other outcomes

There was no change in serum C reactive protein levels over time and no difference between groups (data not shown).

Both treatment groups, on average, gained a small amount of weight (see online supplementary table S2 and supplementary data), with significantly greater weight gain in the high-dose group (p<0.05). As weight gain is a potential mediator of effects on pain and function in knee OA,[34–36] it is plausible that the increased weight gain observed in the high-dose group may have contributed to their poorer WOMAC scores. A post hoc causal

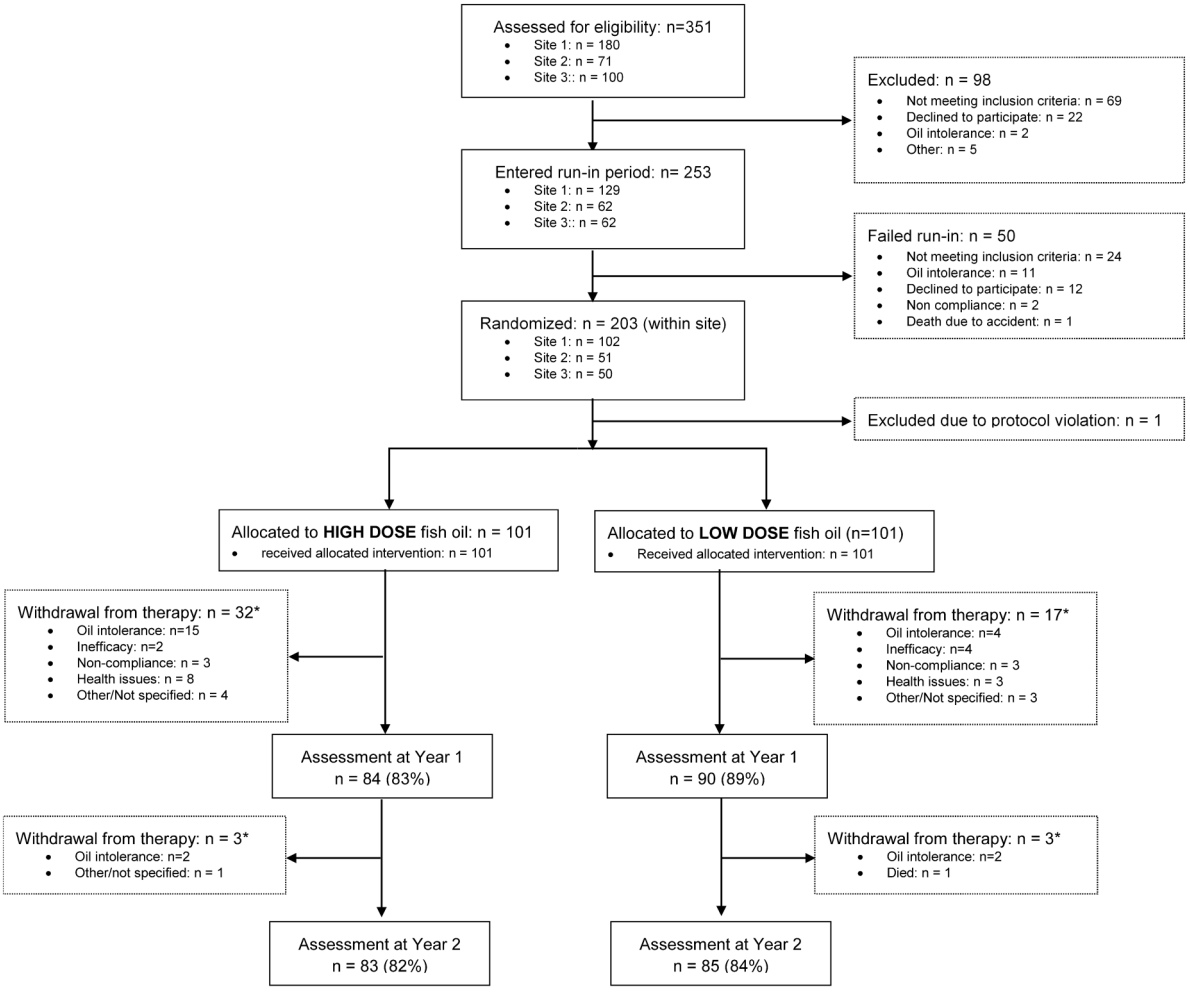


**Figure 1** Flow diagram of participant recruitment and completion.



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**Table 1** Demographic and baseline characteristics

| Characteristic | Low-dose fish oil | High-dose fish oil | p Value |
|---|---|---|---|
| N | 101 | 101 | |
| Age (years): mean (SD) | 61 (10) | 61 (10) | 0.84 |
| Gender (% female) | 40 | 59 | <0.01 |
| BMI (kg/m$^2$): mean (SD) | 29 (4) | 29 (5) | 0.67 |
| WOMAC* pain: mean (SD) | 15 (9) | 16 (9) | 0.35 |
| WOMAC* function: mean (SD) | 49 (29) | 54 (34) | 0.28 |
| Quality of life (AQoL-4D): mean (SD) | 0.77 (0.27) | 0.74 (0.25) | 0.50 |
| NSAID use (%) | 34 | 30 | 0.54 |
| Radiographic knee OA (OARSI%)[20] | 96/101 (95%) | 98/101 (97%) | 0.47 |
| Total OARSI joint space narrowing :mean (SD) | 1.7 (0.1) | 1.8 (0.1) | 0.62 |
| Total OARSI osteophyte score: mean (SD) | 2.0 (0.3) | 2.3 (0.2) | 0.42 |
| MRI Total cartilage volume (μL): mean (SD) | 7.46 (2.09) (n=56) | 6.60 (1.73) (n=60) | 0.02† |
| MRI BML | | | |
| Any BML (%) | 44/55 (82%) | 47/55 (85%) | 0.61 |
| BML size (mm$^2$): median (IQR) | 118 (209) | 122 (219) | 0.70 |
| CRP: median (IQR) | 1.5 (2.2) | 1.7 (2.3) | 0.43 |
| Plasma omega-3 fatty acids | | | |
| Plasma EPA (20:5n-3): mean (SD) | 1.3 (0.7) (n=95) | 1.5 (1.1) (n=94) | 0.17 |
| Plasma DHA (22:6n-3): mean (SD) | 3.4 (1.0) (n=95) | 3.5 (1.2) (n=94) | 0.75 |

*Western Ontario and McMaster Universities Arthritis Index, scored on the NRS 3.1 10-point numerical scale.[21] Pain scores range (0,50) and function scores range (0,170).
†p=0.26 after gender adjustment.
BMI, body mass index; BML, bone marrow lesion; CRP, C reactive protein; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; NRS, numerical rating scale; NSAID, non-steroidal anti-inflammatory drugs; OA, osteoarthritis; OARSI, Osteoarthritis Research Society International; WOMAC, Western Ontario and McMaster Universities Arthritis Index.

mediation analysis determined that weight, as a mediator variable, contributed <1% to the average difference between the high-dose and low-dose treatments (over the six treatment visits) for either pain (p=0.88) or function (p=0.89). It is therefore unlikely that the between-group differences in WOMAC outcomes can be attributed to differences in weight gain.

### Compliance

Assessed by measuring the oil volume in returned bottles, compliance was >80% in both groups. Both groups had increases from baseline in plasma EPA and DHA with the high-dose group having substantially larger increases, consistent with compliance with study oil (figure 2A–C).

### Success of blinding

At the end of the study, 52% of participants were unsure which group to which they had been allocated (50% high dose, 50% low dose). Of the remaining who thought they knew which group they were allocated, only 57% answered correctly, suggesting that blinding had been well maintained.

### Adverse events

Adverse events were common and did not occur more frequently in either group (table 4). Serious adverse events were primarily non-elective hospital admissions. There was a sudden cardiac death in the low-dose group, considered unrelated to the intervention. There were no significant bleeding or thrombosis complications in either group. Although gastrointestinal adverse events were equally common in each group, this led to greater discontinuation of treatment in the high-dose compared with the low-dose group (16.8% vs 5.9%; p<0.015).

## DISCUSSION

This double-blinded randomised clinical trial demonstrated that ingestion of low-dose fish oil (in combination with sunola oil) resulted in better pain and function scores at 18 and 24 months compared with high-dose fish oil. This difference occurred with no change in the use of analgesics or NSAIDs over 24 months. There was no difference in structural outcomes of cartilage volumes and BMLs over 24 months. The study showed no benefit of high-dose fish oil over low-dose fish oil, which was the primary hypothesis of the study. Unexpectedly, the lower dose fish oil group had less pain and better function than the high-dose group. The reasons for this unanticipated result remain unclear. There was greater weight gain in the high-dose group compared with the low–dose group, which may contribute to higher pain scores. However, a post hoc mediator analysis demonstrated this differential weight gain did not influence the difference in pain and function seen between the two groups. The small difference in weight gain is itself difficult to explain, as both groups consumed equivalent volumes of oil, with similar caloric intake.

There was no group difference at 24 months in change in cartilage volume or BMLs. Although MRI data from one site could not be used due to inconsistent MRI sequences, there was no imbalance in the groups due to stratification of randomisation by study site, and there was good follow-up (84%) for MRI data from the other two sites. However, there was loss of power for these endpoints, so it is not possible to make firm conclusions regarding structure modification from our findings.

The comparator oil, which contained predominantly sunola oil, was not expected to have any therapeutic effect. It is low in saturated fatty acids, n-6 fatty acids and n-3 fatty acids, and is predominantly non-essential, monounsaturated oleic acid (n-9). A previous 6-month RCT in OA comparing cod liver oil (rich in omega-3 fatty acids) and olive oil (rich in n-9 fatty acids) demonstrated no difference between the groups after 6 months.[37] However, in contrast to olive oil, sunola oil is not rich in polyphenols with which anti-inflammatory actions have been associated.[38 39] One possible explanation could be that



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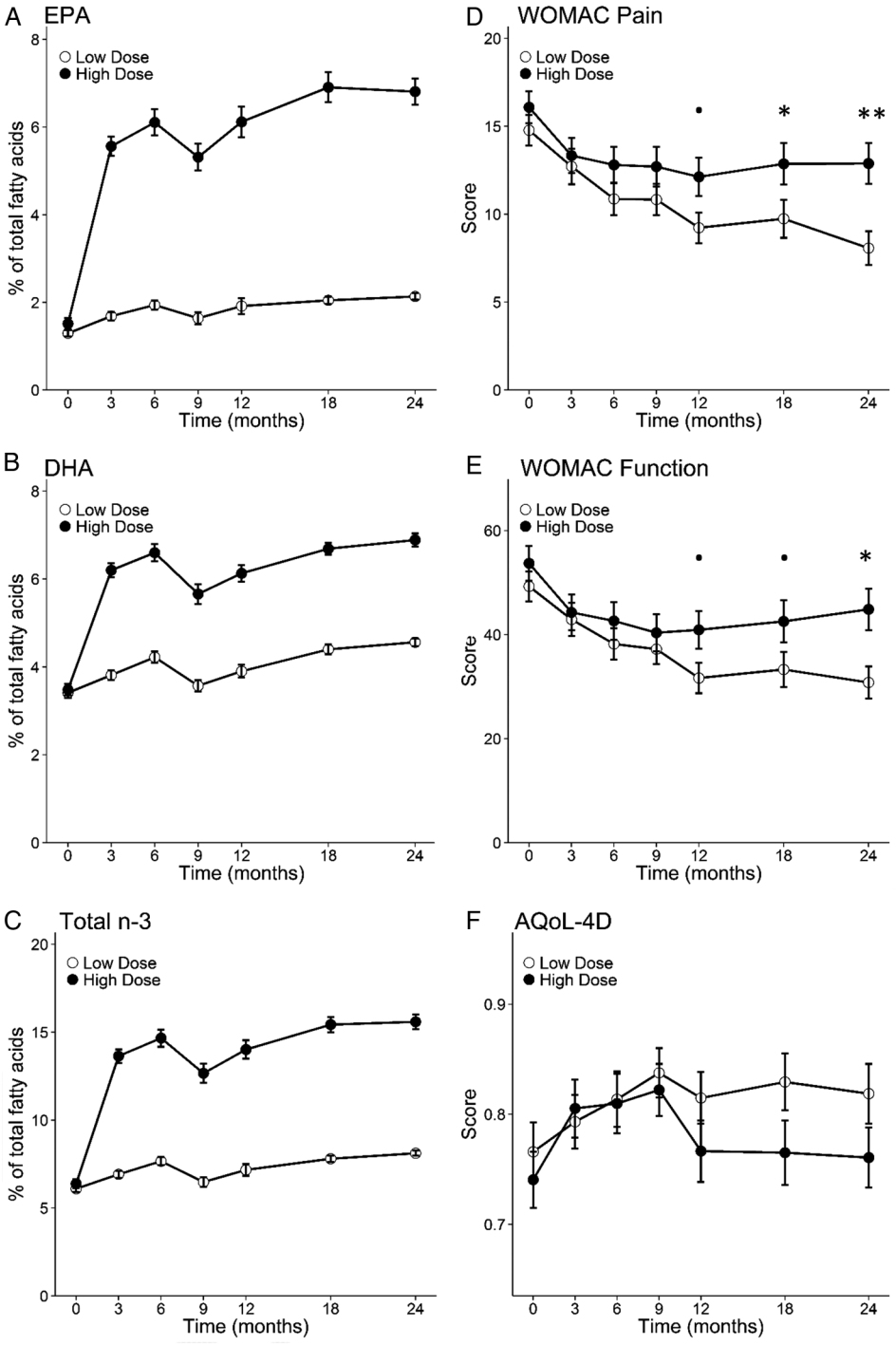


**Figure 2** Mean n-3 fatty acids and osteoarthritis outcomes over the study duration (intention-to-treat patients) for high-dose compared with low-dose fish oil treatment. Vertical error bars represent the SE of the mean. n-3 fatty acids ((A) eicosapentaenoic acid (EPA); (B) docosahexaenoic acid (DHA); and (C) total n-3)) were expressed as a percentage of total fatty acids, and were significantly increased in high-dose compared with low-dose patients at all treatment visits. Western Ontario and McMaster Universities Arthritis Index (WOMAC) outcomes were (D). Pain (numerical rating scale (NRS) 3.1 0–50 scale) and (E) function (NRS 3.1 0–170 scale). Both were significantly higher in the high-dose patients at the end of study (<0.10, *p<0.05, **p<0.01). There were no significant differences between the two treatment groups for quality of life scores ((F) AQoL-4D).

**Table 2** Difference in Western Ontario and McMaster Universities Arthritis Index (WOMAC) outcomes between high-dose and low-dose fish oil at 1 and 2 years, respectively

| | Intention-to-treat | | | | Per protocol | | | |
|---|---|---|---|---|---|---|---|---|
| | High dose—low dose | | | | High dose—low dose | | | |
| | 1 year (n=101) | | 2 years (n=101) | | 1 year (n=80) | | 2 years (n=65) | |
| Outcome | Mean (SE) | p Value | Mean (SE) | p Value | Mean (SE) | p Value | Mean (SE) | p Value |
| WOMAC Pain | 2.3 (1.2) | 0.06 | 3.3 (1.3) | 0.009 | 3.3 (1.2) | 0.007 | 4.1 (1.2) | 0.001 |
| Gender adjusted | 2.1 (1.2) | 0.081 | 3.1 (1.3) | 0.014 | 3.1 (1.2) | 0.009 | 4.0 (1.2) | 0.001 |
| WOMAC function | 6.5 (3.7) | 0.08 | 8.5 (4.0) | 0.032 | 8.4 (3.6) | 0.019 | 11.6 (3.7) | 0.002 |
| Gender adjusted | 5.9 (3.7) | 0.11 | 7.9 (4.0) | 0.046 | 8.0 (3.6) | 0.026 | 11.2 (3.7) | 0.003 |



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**Table 3** Changes in MRI cartilage volume and bone marrow lesion area over 2 years of fish oil treatment

| | Intention to treat | | | Per protocol | | |
|---|---|---|---|---|---|---|
| | Low dose | High dose | p Value | Low dose | High dose | p Value |
| N | 56 | 59 | | 53 | 45 | |
| *Cartilage volume*: proportion with a statistically significant change (least significant change) at 2 years† | | | | | | |
| Decrease | 3 (5%) | 8 (14%) | 0.21* | 2 (4%) | 5 (11%) | 0.09* |
| No change | 47 (84%) | 42 (71%) | | 46 (87%) | 31 (69%) | |
| Increase | 6 (11%) | 9 (15%) | | 5 (10%) | 9 (20%) | |
| *Bone marrow lesions*: proportion with a clinically significant change at 2 years‡ | | | | | | |
| Decrease | 5 (9%) | 7 (13%) | 0.23* | 5 (10%) | 6 (14%) | 0.41* |
| No change | 48 (87%) | 42 (76%) | | 45 (87%) | 33 (77%) | |
| Increase | 2 (4%) | 6 (11%) | | 2 (4%) | 4 (9%) | |

*p Values refer to comparisons between fish oil treatment groups.
†Least significant change[33] was considered a change of >8% in either direction.
‡Clinically significant was considered a change >140 $mm^2$ in either direction, which corresponds to a one-unit change in Western Ontario and McMaster Universities Arthritis Index score.[25]

**Table 4** Number of participants with adverse events

| | Low-dose fish oil | High-dose fish oil |
|---|---|---|
| Hospitalisations | 37 (36.6%) | 38 (37.6%) |
| Infection (all) | 66 (65.3%) | 71 (70.3%) |
| Respiratory | 46 (45.5%) | 51 (50.5%) |
| Ear | 1 (1.0%) | 4 (4.0%) |
| Other | 19 (18.8%) | 16 (15.8%) |
| Gastrointestinal (all) | 62 (61.4%) | 67 (66.3%) |
| Upset | 26 (25.7%) | 15 (14.9%) |
| Reflux | 12 (11.9%) | 17 (16.8%) |
| Nausea | 13 (12.9%) | 19 (18.8%) |
| Diarrhoea | 5 (5.0%) | 8 (7.9%) |
| Intolerance/other | 6 (5.9%) | 8 (7.9%) |
| Bleeding (all) | 4 (4.0%) | 1 (1.0%) |
| Epistaxis | 1 (1.0%) | 0 (0.0%) |
| Haemarthrosis | 0 (0.0%) | 1 (1.0%) |
| Postoperative | 1 (1.0%) | 0 (0.0%) |
| Rectal | 1 (1.0%) | 0 (0.0%) |
| Minor | 1 (1.0%) | 0 (0.0%) |
| Thrombosis (all) | 1 (1.0%) | 1 (1.0%) |
| Superficial leg vein | 1 (1.0%) | 0 (0.0%) |
| Deep vein thrombosis | 0 (0.0%) | 1 (1.0%) |
| Cancer (all) | 9 (8.9%) | 12 (11.9%) |
| Breast cancer | 1 (1.0%) | 1 (1.0%) |
| Prostate cancer | 1 (1.0%) | 0 (0.0%) |
| Non-melanotic skin Ca | 6 (5.9%) | 9 (8.9%) |
| Melanoma | 1 (1.0%) | 0 (0.0%) |
| Other cancer | 0 (0.0%) | 2 (2.0%) |
| Cardiovascular (all) | 16 (15.8%) | 18 (17.8%) |
| Sudden cardiac death | 1 (1.0%) | 0 (0.0%) |
| Acute coronary syndrome | 10 (9.9%) | 10 (9.9%) |
| Palpitations/atrial fibrillation | 4 (4.0%) | 4 (4.0%) |
| Uncontrolled hypo/hypertension | 1 (1.0%) | 3 (3.0%) |
| Pulmonary oedema | 0 (0.0%) | 1 (1.0%) |
| Knee surgery (all) | 5 (5.0%) | 6 (5.9%) |
| Study knee | 2 (2.0%) | 4 (4.0%) |
| Non-study knee | 3 (3.0%) | 2 (2.0%) |

sunola oil with or without low-dose fish may confer a beneficial effect, but this unanticipated finding requires confirmation in further trials.

An alternative explanation is that both groups experienced a 'placebo effect'. Although the changes in pain scores in this study are comparable to those seen with 'placebo effect' for pain,[40] this is difficult to assess in the current study due to lack of control group. The GAIT study, which compared glucosamine, chondroitin, glucosamine/chondroitin, celecoxib and placebo, demonstrated similar improvement in pain in all groups over 2 years. WOMAC pain scores declined in the first 12 weeks with little or no change thereafter.[41] In our study, the WOMAC pain scores in both groups were similar at 3 months then began to diverge with participants in the low-dose group continuing to have reduction after 12 months. The initial reduction in WOMAC scores at 3 months is consistent with regression to the mean. However, it is unlikely that this phenomenon can fully explain the better outcome observed in the low-dose group during the second year of the study.

A study limitation is the lack of a control group. Inclusion of a small amount of fish oil allowed appropriate masking of the oils. This was successful as participants were not able to accurately detect the oil to which they had been randomised. The greater intolerance and greater withdrawal in the high-dose group was unexpected given the run-in period with daily ingestion of liquid oil and the additives of citrus oils, which gave both oils a similar taste. It was considered unethical to prevent fish oil supplements for 2 years in these older, more overweight participants and the 450 mg EPA+DHA daily intake in the low-dose group complies with recommendations aimed at reducing cardiac mortality, which are based on the antiarrhythmic effect of these fatty acids.[42] Anti-inflammatory effects have not been seen at doses this low.[43]

The question arises whether sunola oil may have some efficacy in OA. With hindsight, we believe that the most appropriate control group would have been no oil at all, which would of course sacrifice the ability to perform a blinded study. However, given the study we performed, it is a reasonable conclusion that it is still unknown whether low-dose fish oil and/or sunola oil are beneficial for knee OA.

This was an investigator-initiated rigorously conducted study with excellent 2-year follow-up. The strengths of the study

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include adequate masking of fish oil, repeated symptom measures and MRI imaging. There was a low overall dropout rate for the study despite significant withdrawal due to oil intolerance.

We found no benefit of high-dose fish oil supplementation compared with low-dose fish oil supplementation in knee OA. The unanticipated finding of better pain and function in the low-dose fish oil/sunola group requires further investigation.

**Correction notice** This article has been corrected since it was published Online First. The first name of the sixth author has been corrected and the affiliations for the sixth and last authors have been corrected.

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**Contributors** CLH, LMM, LGC and GJ designed the study and obtained funding. RB, KH and TF recruited participants. CLH, LMM, GJ, RB, KH and TF screened participants. DA read and interpreted MR images. SEL provided statistical analysis and advice. CLH and MJ wrote the draft manuscript. CLH, GJ, LMM, SMP, LGC and MJ participated in data interpretation. All authors critically reviewed and edited the manuscript and approved the final version.

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