Fish oil supplementation reduces osteoarthritis-specific pain in older adults with overweight/obesity

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Short title: fish oil reduces osteoarthritis-specific pain
Abstract

Objectives: Osteoarthritis (OA) is a leading cause of chronic pain and disability. Next to inflammation, vascular pathology has been hypothesised to play a role in its etiology and progression. Due to side effects and low efficacy of pharmacological treatments, dietary supplements are popular as alternative treatments, but evidence of efficacy is limited. We tested whether fish oil and curcumin supplementation can reduce chronic pain and OA burden in older adults.

Methods: A 16-week randomized, double-blind, placebo-controlled, 2x2 factorial design supplementation trial with fish oil (2000mg docosahexaenoic acid + 400mg eicosapentaenoic acid/day), curcumin (160mg/day) or a combination of both was undertaken in sedentary overweight/obese older adults. Secondary outcomes included treatment changes in self-reported chronic pain and OA burden and whether changes are related to changes in small artery elasticity (surrogate marker for microvascular function), C-reactive protein (inflammatory marker) and well-being.

Results: The majority of participants (131/152) reported chronic pain, which was predominantly OA-specific. Fish oil significantly reduced OA-specific pain (P=0.002, Cohen’s d=0.56) and burden (P=0.015, Cohen’s d=0.45) compared to no fish oil treatment; reductions correlated with improvements in microvascular function and well-being. Curcumin, alone or in combination with fish oil, did not reduce pain measures.

Conclusion: Our findings indicate potential for fish oil to alleviate OA pain and burden in overweight/obese older adults. Further investigations should be undertaken in patients with clinically diagnosed OA to evaluate fish oil alone and as an adjunct to conventional pharmacotherapy and to investigate underlying mechanisms.
Clinical Trial Registration: Australian and New Zealand Clinical Trials Register; https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=370788; ACTRN12616000732482p

Key words: osteoarthritis, obesity, fish oil, curcumin, microvascular function

Key messages

- DHA-rich fish oil supplementation alleviated chronic osteoarthritic pain and burden in sedentary overweight/obese older adults.
- The reductions in osteoarthritic pain and burden were accompanied by improvements in well-being.
- Reductions in osteoarthritic pain might be at least partially mediated by improvements in microcirculatory function.

Introduction

Osteoarthritis (OA) is a chronic and progressive condition affecting the whole joint and is characterized by remodelling of the subchondral bone, cartilage damage and inflammation of the synovium tissue and tendon [1]. With 18% of women and 9.6% of men over 60 years affected worldwide, OA is a leading cause of chronic pain and disability in the elderly and the predominant condition for knee and hip replacement, thereby contributing to greater costs and burden on the health care system [2-4]. OA often co-occurs with obesity and they can negatively affect one another, resulting in a vicious cycle due to physical inactivity/disability [5, 6]. Excess weight increases joint loading which, together with the obesity-associated chronic low-grade inflammation and subsequent release of pro-inflammatory cytokines and adipokines, affects the structural integrity of joint bone and cartilage [6]. The link between obesity and OA
might also be partially due to microvascular pathology, which has been hypothesized to play a role in the initiation and progression of joint disease [7, 8]. One hallmark of OA is remodelling of the subchondral bone, which is a highly vascularized tissue. Vascular disease in the subchondral bone is believed to accelerate the OA process due to altered cartilage nutrition and direct ischaemic effects on the bone [7].

Conventional therapy for OA is medication with non-steroidal anti-inflammatory drugs (NSAIDs); however, their therapeutic efficacy is minimal and is limited by side effects associated with long-term use. Therefore, dietary supplements are gaining increasing popularity as an alternative treatment modality [9, 10]. Two of these are fish oil, containing the long-chain omega-3 polyunsaturated fatty acids (LCn-3PUFA) docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), and curcumin, a polyphenolic compound and the main active component of the curry spice turmeric (Curcuma Longa). Fish oil and curcumin are both potent anti-inflammatory bioactive nutrients [11], therefore, benefits for patients with OA are assumed. However, clinical evidence is still inadequate. A meta-analysis by Senftleber et al. concluded that LCn-3PUFAs have favourable effects in rheumatoid arthritis but evidence for OA pain alleviation is of low quality, since only five randomized clinical trials were identified and they had a high risk of bias [12]. For curcumin, clinical trials are also limited in number and focus primarily on knee OA. A meta-analysis by Onakpoya et al. concluded that curcumin supplementation may have some beneficial effects on knee pain, but pain relief is less effective than with ibuprofen [13].

We recently reported the effects of a 16-week supplementation trial of fish oil and/or curcumin on systemic and cerebral vascular function (primary outcome: cerebrovascular responsiveness to hypercapnia) and inflammation (C-reactive protein, CRP) in overweight/obese sedentary older adults [14]. In the same study, effects of
fish oil and curcumin, independently and in combination, on self-reported chronic pain and OA burden were tested and whether any reductions in chronic pain would be 1) related to enhanced microvascular function and reduced inflammation and 2) accompanied by improvements in well-being (including general health perception, mood and depressive symptoms). The aim of this secondary analysis was to provide more clinical evidence on whether fish oil and/or curcumin supplementation could be used as alternative treatment modality for OA pain and burden in a population group at increased risk of developing OA.

Methods

Study design

A 16-week randomized, double-blind, 2x2 factorial, placebo-controlled intervention was undertaken at the University of Newcastle’s Clinical Nutrition Research Centre. Community-dwelling adults residing in the Hunter region of New South Wales aged between 50 and 80 years with overweight or obesity (body mass index (BMI) 25-40 kg/m²) who had a sedentary lifestyle (<150 min of planned physical activity per week) were recruited via approved media advertising (radio interviews, newspaper articles, website advertisements) and by contacting local social groups for older adults. Participants were excluded if their fish/seafood intake exceeded more than two servings per week or more than 300mg/day of LCn-3PUFA from fish oil supplements, had suspected dementia, had been diagnosed with major depression, had a history of cardiovascular, kidney or liver disease or neurological condition, or were on insulin or warfarin therapy. This study was approved by the University of Newcastle’s Human Research Ethics Committee (H-2016-0170), registered with the Australian and New Zealand Clinical Trials Register (ACTRN12616000732482p) and conducted in...
accordance with the International Conference on Harmonization Guidelines for Good Clinical Practice. Written consent was obtained prior to commencement.

An independent investigator allocated participants to one of the four treatment groups according to the Altman’s allocation by minimization method [15] to ensure balanced groups based on age, BMI and sex:

1. Fish oil (FO): total dose of 400mg EPA and 2000mg DHA
2. Curcumin (CUR): total dose of 160mg Longvida® curcumin
3. Fish oil and curcumin (FO+CUR): 400mg EPA, 2000mg DHA and 160mg curcumin
4. Matching placebos (PL):
   a. FO placebo: mix of corn oil and olive with 20mg of fish oil (odour match)
   b. CUR placebo: maltodextrin with yellow food colouring

Capsules were supplied by Blackmores Institute (Sydney, Australia) and were identical in appearance to their respective placebos, identifiable only by code. The active fish oil capsules (Blackmores Omega Brain™) contained 100mg EPA and 500mg DHA each and the active curcumin capsules (Blackmores Brain Active™) contained 400mg Longvida® extract (80mg curcumin). During the 16-week intervention, participants were instructed to consume six capsules daily (two fish oil and one curcumin or matching placebo, both morning and evening with meals) and to maintain their habitual diet and exercise regimen. To facilitate compliance, participants were asked to record each supplement intake in an assigned diary together with any changes in their medication intake and were followed up with a phone call at mid-intervention to enquire about their well-being. At the end of the trial, all remaining capsules were counted to assess overall compliance. Blinding was maintained until all data analysis had been completed.
Study procedures and outcome measures

A detailed description of the study procedures has been published [14]. Briefly, participants attended the research facility for a total of four times (two in the beginning and two at the end of the intervention) having refrained from medication, food and beverages other than water for at least two hours before the visit. During the first visit, anthropometric measures were taken and participants were screened for suspected dementia (<82/100 on the Addenbrooke’s cognitive examination III). Then, participants were seated down for at least 10 minutes before measuring arterial compliance (Cardiovascular Profiler CR2000, Hypertension Diagnostics Inc.). Arterial pulse waveform analysis was used to assess the artery elasticity index of the small arteries, an indicator for endothelial dysfunction. Three consecutive measurements were taken and averaged for analysis. During the second visit, a venous blood sample was collected by a commercial pathology centre after an overnight fast to measure the inflammatory biomarker high-sensitivity CRP. Then, participants were asked to complete questionnaires regarding their chronic pain and OA burden, as well as their general well-being. All assessments were repeated in the same order at the end of the 16-week trial.

Chronic pain measures

The participants’ chronic pain symptoms (>1 month) were captured with the short-form McGill Pain Questionnaire, which consisted of three parts [16]. Firstly, participants were asked to assign an intensity to each of the 15 descriptors of sensory pain using a Likert scale from ‘none’ to ‘severe’ (pain score). Each intensity scale was assigned a numerical value with 45 being the maximum total score, indicating most pain. Furthermore, chronic pain intensity was assessed using a 10 cm visual analogue scale.
(VAS) and a 5-point scale ranging from ‘no pain’ to ‘excruciating’ was used to measure present pain intensity (PPI). Each subscale (pain score, VAS, PPI) score was expressed as a percentage and an average of all subscales was taken to give an overall pain score. Moreover, pain location was captured using a body diagram.

The Osteoarthritis Questionnaire (OA-Quest) was used to assess the impact of chronic pain due to osteoarthritis on participant’s daily life during the last four weeks before their scheduled visit [17]. The questionnaire consisted of 42 statements and included seven dimensions of osteoarthritis burden, i.e. physical distress, sleep disturbance, psychological distress, loss of productivity, physical limitations, physical deconditioning and financial hardship. Participants had to indicate how true each of the statements was for them on a Likert scale from ‘not at all’ to ‘extremely’, with each scale being assigned a numerical value. A sum of all values was taken and expressed as a percentage of the maximum score (168 points), with a higher score indicating more OA-burden.

**Well-being questionnaires**

The participants’ perception of physical and mental well-being during the last four weeks before their scheduled visit was assessed with the 36-Item Short Form Survey (SF-36) which includes nine subscales [18]. Each subscale has a maximum score of 100, indicating no disability, and overall perception of Quality of Life (QoL) was calculated by taking an average of all subscale scores.

The participants’ mood states over the last seven days before their scheduled visit were assessed with the Profile of Mood states questionnaire. The 65 descriptive words were divided into six mood subscales which were each expressed as percentages of their maximum score. The total mood disturbance (TMD) was
calculated by summing the percentages of all subscales (except vigour), divided by the maximum score and then subtracting the percentage obtained for vigour. A more negative TMD percentage indicates better overall mood.

Depressive symptoms were assessed with the Centre for Epidemiologic Studies Depression Scale (CES-D) questionnaire. It consists of 20 statements and participants had to rate the frequency of their experience for each statement during the last seven days before their visit (‘rarely’ to ‘most or all the time’). Each frequency was assigned a numerical score with a maximum score of 60, which was expressed as a percentage. A percentage of 25 and above indicates a risk of depression.

**Statistical analysis**

This is a retrospective exploratory analysis of secondary outcomes in our previously published clinical trial [14]. To detect a 0.7 effect size (Cohen’s d) difference between treatment groups in the primary outcome (CVR to hypercapnia) at alpha = 0.05, an estimated 136 participants were needed.

Using a per-protocol analysis and setting compliance to 80%, differences in changes in chronic pain measures between each treatment group and placebo were determined by ANOVA (IBM SPSS version 24, New York, NY, USA), with baseline pain (model 1) or baseline pain and BMI (model 2) as covariates. Moreover, using the 2x2 factorial design, effects of fish oil and curcumin treatment were assessed independently:

- Fish oil (FO and FO+CUR group) vs. no fish oil (CUR and PL group)
- Curcumin (CUR and FO+CUR group) vs. no curcumin (FO and PL group)

Pearson’s correlation analysis was used to determine whether changes in chronic pain symptoms were related to changes in the small artery elasticity index (used herein as
a surrogate marker of the microvasculature), CRP, quality of life, overall mood and depressive symptoms. All results are presented as mean ± standard error of mean.

Results

Participants and baseline pain measures

Between June 2017 and August 2018, 152 participants were enrolled, of which 134 completed the intervention and after setting the compliance to 80%, 126 participants remained (for CONSORT diagram see Kuszewski et al. [14]). Side effects were reported in four participants (digestive problems: PL n=1, CUR n=1, FO+CUR n=1; reflux: PL n=1), but no serious adverse events were reported. Two participants were excluded from the pain analysis (PL n=1, FO+CUR n=1), due to un-related pain that was non-existent at baseline (shingles), leaving 124 participants for analysis (PL n=31, FO n=32, CUR n=31, FO+CUR n=30).

Participants’ baseline characteristics are described in Table 1. Chronic pain measures were not significantly different between groups except for OA burden, which was significantly lower in the fish oil group compared to the curcumin group (P=0.021). One hundred and thirty one participants (86%) reported chronic pain (McGill Pain questionnaire) at baseline. For the majority (70%), however, pain symptoms were mild, as determined by VAS, averaging 3.5±0.2/ 10cm [19]. The pain was mostly OA-specific, since it was predominantly reported in knees (41%), lower back (39%) and shoulders (31%), with ‘aching’ being the most common pain descriptor (83%). Furthermore, overall pain and pain subscales correlated strongly with OA burden, with most participants reporting physical deconditioning/limitation (reduction of physical exercise, difficulties with stairs), sleep disturbance and physical distress (weakened joints) (OA-Quest).
Participants with greater chronic pain symptoms and OA burden had a higher BMI, lower QoL and more depressive symptoms and mood disturbance. However, pain symptoms and OA burden were independent of inflammation (CRP).

**Treatment changes in measures of pain**

Fish oil supplementation for 16 weeks significantly reduced pain score and PPI (both $P=0.012$, Cohen’s d=0.65) compared to placebo, resulting in a 42% reduction of overall chronic pain ($P=0.013$, Cohen’s d=0.64) (**Table 2**). Furthermore, it tended to reduce the OA burden by 40% ($P=0.052$, Cohen’s d=0.49), which reached significance after adjusting for baseline BMI (model 2; $P=0.050$, Cohen’s d=0.50, compared to placebo). In contrast, curcumin supplementation did not affect any chronic pain measures. The combination of fish oil and curcumin tended to reduce chronic pain measures, however, only the reduction of PPI was significant ($P=0.041$, Cohen’s d=0.12).

Utilizing the 2x2 factorial analysis, fish oil treatment significantly reduced pain score ($P<0.001$, Cohen’s d=0.85), PPI ($P=0.003$, Cohen’s d=0.54) and overall pain ($P=0.002$, Cohen’s d=0.56), as well as OA burden ($P=0.015$, Cohen’s d=0.45) compared to no fish oil treatment (**Figure 1**). The reduction in overall pain and OA burden in participants supplemented with fish oil was greater in those who reported higher baseline pain/ OA burden at baseline ($n=62$; pain: $R=-0.528$, $P<0.001$, OA burden: $R= -0.548$, $P<0.001$).

The reductions in overall pain following fish oil treatment were associated with increases in small artery elasticity index (**Figure 2**, FO group only, $n=32$: $R= -0.560$, $P=0.001$; FO 2x2 factorial design, $n=62$: $R= -0.296$, $P=0.022$), but not with changes in CRP ($n=62$, $R= -0.167$, $P=0.211$).
Treatment changes in pain measures reported above include all participants that finished the intervention with a compliance of >80%. We also performed a separate analysis with only those participants who reported chronic pain at baseline (n=131), but the outcomes were unaffected.

**Correlations between changes in chronic pain and changes in well-being**

The reduction in overall pain correlated with reductions in TMD (R=0.239, P=0.009) and depressive symptoms (R=0.242, P=0.007) (Figure 3). Furthermore, the reduction in overall pain tended to correlate with better perception of total health (QoL) (R=-0.177, P=0.055) and correlated significantly with perception of physical health (R=-0.188, P=0.040). Similar correlations were observed between changes in OA burden and TMD (R=0.270, P=0.003), depressive symptoms (R=0.286, P=0.001) and QoL (R=-0.336, P<0.001).

**Discussion**

In this exploratory analysis, 16 weeks of supplementation with DHA-rich fish oil but not curcumin reduced mild chronic pain symptoms - which were predominantly OA-specific - as well as OA burden in overweight/obese sedentary older adults. These reductions were accompanied by enhanced well-being, i.e. reductions in mood disturbance and depressive symptoms and an improvement in physical health perception, independent of changes in BMI.

**Potential mechanisms underlying the pain-reducing effects of fish oil**

Current treatments for OA target inflammation, as OA is associated with increases in several pro-inflammatory cytokines, such as interleukin-1 (IL-1), that are involved in
cartilage degradation, which is one of the causes of OA pain symptoms [20, 21]. Due to the well-known anti-inflammatory effects of fish oil [22], it was expected to be beneficial in OA treatment [10]. However, since 1989 only five studies have examined the effect of marine oils (containing LCn-3PUFA) on OA-specific pain, of which three showed slight reductions in pain, but the quality of those studies was very low due to high risk of bias [12]. The studies examined CRP levels, but found no significant treatment changes. There is evidence from in vitro studies showing that fish oil can reduce IL-1 in bovine chondrocytes and decrease inflammation-induced destruction of tissue in human osteoarthritic cartilage harvested during surgical procedures [10]. In our study, fish oil supplementation slightly reduced the inflammatory marker CRP [14] but the reduction was not significant and did not correlate with a reduction in pain symptoms. However, one limitation of this study is that we did not measure other inflammatory markers involved in OA, such as IL-1 or tumor necrosis factor alpha (TNF-α), which might have been more sensitive. Furthermore, participants reported mild chronic pain and OA burden and CRP levels were only slightly elevated (<3mg/L), suggesting that their OA was still in the early stages with minimal cartilage degradation. Further well-designed studies are needed in participants with higher CRP levels and more advanced radiographic and symptomatic OA to test the hypothesis that fish oil reduces OA pain by counteracting inflammation.

Another cause of pain in OA is the reduction in blood flow due to vascular disease and consequent damage to the microvasculature between the articular cartilage and subchondral bone [7, 21]. Impaired blood perfusion of tissues can cause ischemic pain, mediated by the loss of oxygen and nutrient supply to nerves; thus restoring blood flow is a promising treatment target for pain relief in OA [21]. Our finding of a correlation between reductions of chronic OA-specific pain following fish oil supplementation and
increases in small artery elasticity index suggests that fish oil’s ability to alleviate pain might be at least partly attributable to improved microvascular function. The endothelium is the key regulator of blood flow and endothelial dysfunction is characterised by impaired nitric oxide production or availability, leading to impaired endothelium-dependent vasodilatation [23]. Fish oil can improve endothelial function by increasing production of the vasodilators nitric oxide and prostacyclin, decreasing production of the vasoconstrictor endothelin-1 and reducing oxidative stress [24]. Clinical trials have shown that fish oil supplementation can enhance flow-mediated dilatation (FMD), a marker of endothelial function [25]. The improved endothelium-dependent vasodilatation following fish oil supplementation might improve perfusion to previously hypoxic tissues, restoring the oxygen and nutrient supply in affected joints, thereby reducing ischemic pain [21].

**Lack of effect following curcumin supplementation**

There is evidence that curcumin inhibits inflammation in bovine and human chondrocytes and human clinical trials have shown slight reductions in knee OA pain, although the efficacy was lower compared to ibuprofen [13]. In our study, curcumin supplementation did not affect OA-specific pain or OA burden in overweight/obese older adults. One possible reason might be that the OA pain and burden in our study population was too mild. The previous studies were performed in patients with established OA associated with more severe pain [13]. When we explored the effects of curcumin in a sub-group of participants with moderate-severe pain (n=35, VAS: 4.6-9.4cm), curcumin elicited a slight, non-significant reduction in pain as opposed to a non-significant increase in pain seen in participants with mild chronic pain (n=88, VAS<4.5cm). This suggests that curcumin might have potential benefits in adults with
moderate-severe OA pain but could be disadvantageous in adults with mild OA pain. Furthermore, it should be noted that previous studies were limited to knee OA while our study looked at general OA pain, although knee pain was most common. Further investigations are required to identify OA patients who might benefit from curcumin supplementation based on pain severity, location and possibly absence/presence of metabolic disorders.

**Combination of fish oil with other nutrients or medication**

The combination of fish oil and curcumin did not result in additional OA pain relief and actually seemed to dampen the reduction of OA pain and burden observed with fish oil alone. Combining fish oil with curcumin for additional benefits is a very new approach; clinical trials are limited with inconsistent results [14, 26-28] and effects on OA pain relief have not been tested yet. In migraine patients, fish oil and curcumin were found to have synergistic effects on reduction of inflammatory markers [26, 27] and migraine attack frequency [27]. However, in people at high risk of developing type 2 diabetes, the combination did not result in any complementary effects on glycaemic control and blood lipids [28] and in our study we did not find any synergistic effects on cardiometabolic risk factors and cerebrovascular function [14]. Further studies are warranted to understand the interaction between fish oil and curcumin in humans and ascertain whether 1) there is a specific dose combination for fish oil and curcumin for synergistic effects and 2) it is beneficial only in specific population groups (i.e. migraine patients).

Clinical trials investigating the combination of fish oil with other supplements or NSAIDs for the reduction of OA symptoms are very limited. Fish oil combined with glucosamine – another popular supplement for OA treatment – did not result in greater

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pain reduction compared to glucosamine alone [29]. The potential of fish oil as an adjunct to NSAID medication for OA pain relief has been tested in two clinical trials, one of which found no significant benefit [30] while the other was poorly designed with no placebo control and no monitoring of fish oil supplementation [31]. Thus, further well-designed trials should be undertaken to evaluate fish oil’s potential as an adjunct to pharmacological treatment to achieve greater pain relief and reduce the dose of medication required and associated side effects.

**Study limitations and future directions**

It is important to note that this is an exploratory analysis of secondary outcomes from a large-scale randomized controlled trial. Thus, participants were not recruited based on presence or intensity of OA pain and the study was not powered to detect a difference in pain reduction. Moreover, it should be noted that OA was not diagnosed based on radiographic findings. In this study, we used the short-form McGill questionnaire, which has been shown to be sensitive to demonstrate changes in pain due to treatment [32], to measure the quality, intensity and location of general chronic pain (lasting > 1 month). The description and location of chronic pain indicated whether the reported pain was osteoarthritis-related, which was then further confirmed with the OA-Quest (if participant had no pain or other non-osteoarthritic-related pain, the OA-Quest score was 0%). The OA-Quest furthermore gave important information on how the osteoarthritis-related pain impacts participants’ daily life.

Another limitation is that the basal self-reported OA pain and burden was mild in the majority of participants. Nevertheless, we still observed a reduction in OA-specific pain and burden following fish oil supplementation, which was accompanied by improvements in well-being. Thus, supplementing the diet with fish oil might offer a
potential intervention in individuals who are in an early OA stage to potentially prevent further OA progression. However, further studies are needed to confirm the promising OA pain-reducing effects of fish oil. These should be conducted in individuals with clinically diagnosed OA with pain symptoms ranging from mild to severe and have longer intervention periods (>6 months) with more frequent assessments of pain, especially in the beginning of the trial, to examine 1) at what point in time pain reduction commences, 2) if pain reduction is sustained long-term and 3) at which stage of OA progression individuals benefit most from fish oil supplementation.

Conclusions

Our findings indicate potential for fish oil supplementation to reduce mild OA pain and burden in sedentary overweight/obese older adults with self-reported OA-specific pain, which was associated with improved well-being. The pain alleviating effects of fish oil might be mediated at least partly by improvements in microvascular function. Further studies are warranted to 1) evaluate benefits of DHA-rich fish oil, alone or as an adjunct to pharmacotherapy, in patients diagnosed with OA who suffer moderate-severe pain, 2) investigate mechanisms underlying the potential pain-reducing effects of DHA-rich fish oil and 3) identify OA patients that might benefit from curcumin supplementation.
Acknowledgements

The authors wish to thank Hamish Evans and Natasha Baker for their assistance with the study.

Funding: This study was sponsored by Blackmores Institute (research and education division of Blackmores Ltd.) who provided funding and the test materials but had no role in the study design, data collection, analysis and interpretation or writing of the manuscript.

Disclosure: The authors have declared no conflicts of interest.

Author contributions: R.H.X.W. and P.R.C.H. conceived the study design, J.C.K. recruited the participants, collected and analysed the data and drafted the manuscript under supervision from R.H.X.W. and P.R.C.H. All authors read and approved the final manuscript.
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### Tables

**Table 1.** Participants’ baseline characteristics per group and their correlations with overall pain and OA burden at baseline.

| Characteristics                          | Placebo (n = 36) | Fish oil (n = 39) | Curcumin (n = 38) | Fish oil + curcumin (n = 39) | Overall pain | OA burden |
|------------------------------------------|------------------|-------------------|-------------------|-----------------------------|--------------|-----------|
| Age (years)                              | 65.4 ± 1.3       | 65.4 ± 1.2        | 65.4 ± 1.2        | 66.2 ± 1.3                  | -0.161       | -0.124    |
| BMI (kg/m²)                              | 31.0 ± 0.7       | 31.0 ± 0.7        | 30.5 ± 0.7        | 30.9 ± 0.6                  | 0.356        | 0.288     |
| Waist (cm)                               | 105.4 ± 2.0      | 105.5 ± 1.6       | 103.8 ± 2.0       | 104.4 ± 1.8                 | 0.291        | 0.254     |
| Physical activity (min/week)             | 33.8 ± 9.7       | 55.1 ± 12.8       | 44.4 ± 13.0       | 54.6 ± 14.3                 | -0.066       | -0.155    |
| C-reactive protein (mg/L)                | 2.2 ± 0.4        | 2.3 ± 0.3         | 2.6 ± 0.5         | 2.3 ± 0.2                   | 0.149        | 0.144     |
| Quality of life (score/100)              | 70.4 ± 2.4       | 72.5 ± 1.9        | 67.1 ± 2.5        | 69.4 ± 2.4                  | -0.610       | -0.663    |
| Depressive symptoms (%)                  | 13.4 ± 1.9       | 14.0 ± 1.7        | 17.0 ± 2.1        | 15.4 ± 2.4                  | 0.379        | 0.510     |
| Total mood disturbance (%)*              | -40.1 ± 3.6      | -33.7 ± 4.6       | -28.7 ± 4.2       | -33.0 ± 5.0                 | 0.259        | 0.362     |
| Overall pain (%)                         | 25.5 ± 3.3       | 21.0 ± 2.0        | 25.1 ± 3.1        | 22.9 ± 2.5                  | 0.714        | <0.001    |
| Pain score (%)                           | 13.7 ± 2.4       | 9.6 ± 1.4         | 14.6 ± 2.9        | 12.4 ± 2.4                  | 0.698        | <0.001    |
| VAS (%)                                  | 34.4 ± 5.0       | 26.2 ± 3.1        | 33.8 ± 4.0        | 29.7 ± 3.7                  | 0.637        | <0.001    |
| PPI (%)                                  | 28.3 ± 3.2       | 27.2 ± 2.5        | 26.8 ± 3.6        | 26.7 ± 2.9                  | 0.580        | <0.001    |
| OA burden (%)                            | 11.2 ± 2.6       | 5.8 ± 1.2         | 12.6 ± 2.4        | 9.8 ± 1.8                   |              |           |

OA: Osteoarthritis, PPI: present pain intensity, VAS: visual analogue scale. A greater negative value (max. -100) indicates better overall mood. Data presented as mean ± standard error of mean.
Table 2. Treatment change in individual outcome measures of pain, expressed as percentages, per group.

|                | Placebo (n = 31) | Fish oil (n = 32) | Curcumin (n = 31) | Fish oil + curcumin (n = 30) |
|----------------|------------------|-------------------|-------------------|-------------------------------|
| Overall pain   |                  |                   |                   |                               |
| Model 1        | -0.4 ± 2.4       | -8.9 ± 2.4        | 2.9 ± 2.4         | -3.5 ± 2.4                    |
| Model 2        | -0.4 ± 2.4       | -8.9 ± 2.4        | 3.0 ± 2.4         | -3.5 ± 2.4                    |
| Pain score     |                  |                   |                   |                               |
| Model 1        | 0.2 ± 1.5        | -5.4 ± 1.6        | 3.4 ± 1.6         | -4.3 ± 1.6                    |
| Model 2        | 0.2 ± 1.5        | -5.4 ± 1.6        | 3.3 ± 1.6         | -4.4 ± 1.6                    |
| VAS            |                  |                   |                   |                               |
| Model 1        | 1.9 ± 3.7        | -7.4 ± 3.7        | 2.9 ± 3.7         | -1.6 ± 3.8                    |
| Model 2        | 1.9 ± 3.7        | -7.5 ± 3.8        | 3.0 ± 3.7         | -1.5 ± 3.8                    |
| PPI            |                  |                   |                   |                               |
| Model 1        | -2.8 ± 3.0       | -13.7 ± 3.0       | 2.4 ± 3.0         | -4.9 ± 3.1                    |
| Model 2        | -2.9 ± 3.0       | -13.8 ± 3.0       | 2.6 ± 3.0         | -4.8 ± 3.0                    |
| OA burden      |                  |                   |                   |                               |
| Model 1        | 1.0 ± 1.2        | -2.3 ± 1.2        | 0.6 ± 1.2         | -2.0 ± 1.2                    |
| Model 2        | 1.0 ± 1.2        | -2.4 ± 1.2        | 0.6 ± 1.2         | -2.0 ± 1.2                    |

OA: Osteoarthritis PPI: present pain intensity, VAS: visual analogue scale. Model 1: adjusted for baseline pain, Model 2: adjusted for baseline pain and body mass index. Data presented as mean ± standard error of mean. Bold values indicate statistically significant from placebo (P < 0.05).
Figure legends

Figure 1. Treatment changes in individual pain measures following fish oil vs. no fish oil treatment. Baseline pain and BMI used as covariates; n = 62 per group. OA: Osteoarthritis PPI: present pain intensity, VAS: visual analogue scale.

Figure 2. Correlation between change in overall pain and small artery elasticity in participants randomised to fish oil. (n=32).

Figure 3. Correlation between change in A) total mood disturbance and B) depressive symptoms and overall pain. (n=121).
Figure 1. Treatment changes in individual pain measures following fish oil vs. no fish oil treatment. Baseline pain and BMI used as covariates; n = 62 per group. OA: Osteoarthritis PPI: present pain intensity, VAS: visual analogue scale.
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R = 0.560
P = 0.031
Figure 3. Correlation between change in A) total mood disturbance and B) depressive symptoms and overall pain. (n=121).

18x29mm (300 x 300 DPI)