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Circulating polyunsaturated fatty acids and pain intensity in five chronic pain conditions

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Abstract

Pain intensity is well-known to be influenced by a wide range of biobehavioral variables. Nutritional factors, however, have not been generally considered for their potential importance. This cross-sectional study examined associations between erythrocyte omega-6 (n-6) and omega-3 (n-3) polyunsaturated fatty acids (PUFAs) and pain intensity in 605 adults. Pain intensity was computed on a 0–100 numeric rating scale from questions about five chronic pain conditions: orofacial pain, headache, low back pain, irritable bowel syndrome, and bodily pain. For each pain condition, multiple linear regression tested the hypothesis that a higher ratio of n-6 arachidonic acid to the sum of n-3 eicosapentaenoic acid and docosahexaenoic acid (AA/(EPA+DHA) was

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Author contributions

AS conducted the analysis and drafted the manuscript. GS, RF and RO were site investigators of the parent study named OPPERA. BE, DW and PS completed the fatty acids LCMS analyses. All authors were involved in the interpretation of data, critically revised and edited the manuscript. All authors approved the final version and take responsibility for data integrity and accuracy of the data analysis.

associated with greater pain intensity. In covariate-adjusted analysis, orofacial pain intensity increased 5.7 points (95% CI: 1.4, 9.9) per unit increase in n-6/n-3 PUFA ratio. Likewise, a one unit increase in n-6/n-3 PUFA ratio was associated with significant increases in pain intensity (range 5–8 points) of headache pain, low back pain, and bodily pain, but not abdominal pain. Separate multiple linear regression models investigated the independent strength of association of individual PUFAs to the intensity of each pain condition. Overall, n-3 docosahexaenoic acid was most strongly, and inversely, associated with pain intensity.

Keywords

Pain intensity; Epidemiology; Chronic overlapping pain conditions; Polyunsaturated fatty acids; Lipidomics

INTRODUCTION

During the twentieth century, consumption of omega-6 (n-6) polyunsaturated fatty acids (PUFAs) in Western diets increased dramatically, initially spurred by aggressive marketing of vegetable oils to replace animal fats[1], and reinforced by the diet-heart hypothesis. This argued that the high levels of n-6 linoleic acid in vegetable oils reduced blood cholesterol and, by extension, reduced heart disease risk.[40] Within a few decades, per capita consumption of margarine increased 10-fold.[5] Over the same period, consumption of fatty fish, the main dietary source of omega-3 (n-3) PUFAs decreased.[5] As a result, the dietary intake of n-6 to n-3 fats shifted from an optimal ratio of 5:1, to 20:1, or even higher.[41]

The imbalanced PUFA intake has consequences for health. The n-6 parent essential fatty acid LA and the n-3 parent essential fatty acid alpha-linolenic acid (ALA) are precursors of signaling molecules with opposing properties. Preclinical[7, 9, 13, 14] and clinical studies[16,20,23,30] show that LA, and its long-chain derivative arachidonic acid (AA) are predominantly proinflammatory, pronociceptive and anxiogenic, whereas ALA and its long chain derivatives eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are anti-inflammatory, proresolving, antinociceptive and anxiolytic. In principle, diets excessively high in n-6 PUFA intake relative to n-3 intake should increase risk for chronic pain. Our own studies showed that adults with a higher n-6/n-3 long-chain PUFA ratio in erythrocytes had lower pressure pain thresholds,[35] greater psychological distress,[36] and higher odds of chronic TMD.[34]

Pain intensity is an important dimension of pain that reflects the magnitude of felt pain.[18] Not only do pain intensity ratings capture the personal nature of pain, their simplicity of use, reliability of measurement, and sensitivity to intervention make them the gold standard in pain outcomes assessment.[11] Consequently, randomized controlled trials (RCTs) of pain treatments often use change in pain intensity as the primary endpoint.[19]

[1]Schleifer D. The Perfect Solution: How Trans Fats Became the Healthy Replacement for Saturated Fats. Technology and Culture; 53(1), January 2012, pp. 94–119. The Johns Hopkins University Press. DOI: 10.1353/tech.2012.0018

Despite its wide use in experimental and observational studies, pain intensity is rarely a criterion in determining pain case classifications. More salient to case classifications are the anatomic structures involved and the frequency of pain episodes. For instance, the case classification for low back pain specifies pain localized below the costal margin and above the inferior gluteal fold.[21] And primary headache is classified as headache that occurs on at least 15 days per month with daily pain duration of least 2 hours.[3] Consequently, a group of people exist who may have quite intense pain, but because their symptoms fail to meet case classification criteria, they are excluded from pain studies and opportunities are missed to learn about this sub-clinical group.

This cross-sectional study did not exclude community dwelling adults in pain whose symptoms did not meet formal pain case classifications. Our objective was to quantify associations between the imbalance in circulating PUFAs, expressed as the ratio of n-6 to n-3 PUFAs, and pain intensity. The first aim was to determine the association between the n-6/n-3 PUA ratio and intensity of painful orofacial pain, headache, low back pain, abdominal pain, and bodily pain. The second aim was to identify which of the individual components of the long-chain PUFA ratio (n-6 AA, n-3 EPA, n-3 DHA) and their short-chain precursors (n-6 LA and n-3 ALA) were most strongly associated with pain intensity.

MATERIALS AND METHODS

Study design, setting, participants

This study used cross-sectional data from OPPERA-II, the second phase of the Orofacial Pain Prospective Evaluation and Research Assessment (OPPERA) study.[43] In its first phase, OPPERA recruited 1,008 people with painful temporomandibular disorder (TMD) and 3,258 TMD-free controls to identify risk factors for TMD.[2, 42] Study participants were a community-based sample of volunteers aged 18 to 44 years from communities near academic health centers in Baltimore, MD; Buffalo, NY; Chapel Hill, NC; and Gainesville, FL between 2006 and 2013.

The second phase of OPPERA (OPPERA-II), conducted between 2014 and 2016, entailed follow-up of 543 OPPERA participants along with an additional 127 adults aged 18–74 years with recent-onset TMD who were recruited from the same four communities. One objective of OPPERA-II was to study the overlap of painful TMD with pain conditions that commonly coexist with TMD. All participants underwent clinical examinations and completed standardized questionnaires and a venous non-fasting blood draw. This current study used data and biospecimens from OPPERA-II participants. The study was reviewed and approved by the UNC Office of Human Research Ethics (study 13–2232). All study participants verbally agreed to a screening interview done by telephone and provided informed, signed consent for all other study procedures.

Pain screening questions

A screening questionnaire in OPPERA-II asked about symptoms from each of five pain conditions in the previous three months. Those who responded affirmatively to screening questions were then asked about intensity of pain for that condition. Orofacial pain screening

asked about symptoms typical of painful TMD: pain the face; pain in the jaw; pain in their ear, pain in front of their ear; headache in their temples; or pain in their temples other than headaches. The headache screener asked participants if they had experienced had any headaches. The lower back pain screener directed participants to a shaded area on the lower back of a body manikin and asked if they had had pain in that area, that was not due to feverish illness or menstruation. The abdominal pain screener asked how often participants had discomfort or pain anywhere in the abdomen, with responses recorded on a seven-point ordinal scale of frequency that ranged from “never” to “every day”. The bodily pain screener asked whether participants had experienced aches or pains anywhere that lasted a day or longer.

Pain intensity assessment

Participants rated the intensity of their pain for each condition in which they screened positive. Ratings were made on an 11-point numerical rating scale anchored at zero “No pain” and 10 “Pain as bad as it could be”. Three aspects of pain intensity were evaluated: pain at the present time; the worst pain, and the average pain over the prior three months. A single overall score was computed by calculating the mean value of these three scores and multiplying it by 10. This yielded a continuous variable with potential range of 0 to 100 that reflected the overall magnitude of the pain. When screening pain symptoms were negative for a pain condition, pain intensity for that pain condition was assigned a value of zero.

Formal case classification for each pain condition

Participants with orofacial pain symptoms were assessed for the presence or absence of painful temporomandibular disorder in a clinical examination using Diagnostic Criteria for Temporomandibular Disorder[37] as described in OPPERA II by Ohrbach.[27]

Participants with headache symptoms were asked further questions to classify presence or absence of tension-type headache and migraine based on questions from the International Classification of Headache Disorders, third edition (ICHD-3)[17] and the ID-Migraine questionnaire[24] described in OPPERA II by Ohrbach.[27] Participants with lower back pain symptoms were asked questions developed by Dionne and colleagues[10] to determine their case classification for low back pain. Participants with abdominal pain symptoms were assessed for irritable bowel syndrome using the ROME III diagnostic criteria[45] as described in OPPERA II by Ohrbach.[27] Participants with bodily pain symptoms were asked to locate these areas on a body manikin, answer more detailed questions, and complete a clinical examination to determine presence or absence of fibromyalgia consistent with the 1990 American College of Rheumatology criteria[47] as described in OPPERA II by Ohrbach.[27]

Covariates

Covariates were selected based on prior knowledge of associations with fatty acids and pain states. OPPERA-II study site was included because it was the basis for sampling participants. Sex was included because of sex differences in the biosynthesis of ALA to EPA and DHA[46] and because women are generally more pain sensitive than men.[46] Age was included because age modifies the association between pain intensity and pain inference in orofacial pain patients.[6] Because of racial differences in PUFA

metabolism and pain prevalence, we distinguished between categories of white and African American participants, and pooled other groups because of their low enrollment numbers. Socioeconomic indicators varied little in OPPERA's study population, so socioeconomic variables were not included. Obesity was included because high levels of n-6 increase risk for obesity, and because obesity is strongly associated with an imbalanced n-6/n-3 PUFA ratio and several of the selected pain conditions. Standardized equipment measured weight and height during clinical examinations. Body mass index (BMI) was calculated by dividing weight in kilograms by the square of height in meters.

Blood sample

At the OPPERA-II study visit, a non-fasting 20 ml sample of circulating blood was obtained by venipuncture and collected into tubes containing EDTA that were promptly centrifuged for 10 min at 4°C. After removing the supernatant plasma, erythrocytes were washed with sodium perborate, vortexed and again centrifuged. After removing the sodium perborate supernatant, erythrocytes were aliquoted into 400 uL cryotubes prior to storage at −80oC.

Polyunsaturated fatty acids

The exposure of interest was PUFAs in circulating erythrocytes. The PUFAs studied were linoleic acid (LA; 18:2n–6), arachidonic acid (AA; 20:4n–6), α-linolenic acid (ALA; 18:3n–3), eicosapentaenoic acid (EPA; 20:5n-3) and docosahexaenoic acid (DHA; 22:6n-3). From these we calculated the ratio of the long-chain n-6/n-3 PUFAs, i.e., those with 20 or 22-carbon atoms, as AA/(EPA+DHA).

Sample preparation and LC-MS/MS analysis

Red blood cells were obtained and stored at −80°C until extraction. To 150 μL of red blood cells, 1 mL of 90:10 methanol to water was added. Samples were vortexed then centrifuged at 20,000 rcf for 10 minutes. The supernatant was dried down and resuspended in 150 μL of 90:10 methanol to water containing deuterated internal standards (50 ng/mL). Two quality control standards with known concentrations (20 and 500 ng/mL) as well as the deuterated internal standard mixture were analyzed at twice per batch of 96 samples to ensure accuracy and reproducibility. The calibration curve was analyzed twice per batch of 96 samples and averaged to include error across the analysis, using standard deviation as error bars.

Analysis was conducted using a Waters Acquity Ultra-Performance Liquid Chromatography system tandem to a ThermoScientific TSQ Vantage. Separations were performed on a 150 mm × 2.1 mm BEH C18 with a flow rate of 0.25 mL/min and an injection volume of 10 μL. Initial mobile phase composition was 65% A (water with 30 mM ammonium formate) and 35% B (80% acetonitrile 20% methanol). A linear decrease was performed to 45% A at 2 min with a hold for 1 min followed by another decrease to 20% A at 7 min. Another slight decrease was performed to 5% A at 8 min and lastly at 10 min to 0% A. The gradient was returned to 65% A at 13 min and held for 3 min for a total of 16 min.

Single reaction monitoring (SRM) was performed in negative mode. The peak width was set to 0.7 Da with a scan time of 0.05 sec per transition. The transitions are provided in Supplementary Table 1. The source conditions were as follows: spray voltage 3200 V, sheath

gas 50 units, auxiliary gas 15 units, and capillary temp 270°C. Analytes with their class, limit of detection (LOD), and limit of quantitation (LOQ) are reported in Supplementary Table 2.

This method separates several isobaric species and allows for a simultaneous quantitation of key n-6 and n-3 PUFAs as well as their derived lipid mediators. The method achieves excellent resolution and allows for accurate quantitation in biological matrices. The method was characterized using human plasma with good linearity (R=0.994–0.999), reproducibility (relative standard deviation (RSD) <15% for most analytes), accuracy (79.2–165.3) for all analytes except prostaglandin E2 and linoleic acid, and recovery (30–74%) for all analytes. The RSD for PGE2 was 62% for both the 20 and 500 ng/mL quality controls (QC). For LA, the RSD for the 20 ng/mL QC was 0.7% and for the 500 ng/mL QC was 77%. All standard measurements were reproducible with RSD<15%.

Statistical analysis and power calculation

We omitted observations from analysis for 28 participants with unreported race/ethnicity status, BMI or smoking status. Also omitted were 7 participants with biospecimens that produced no signal for LA, AA, EPA and DHA and 2 other participants with biospecimens having levels of LA or DHA below the limit of quantitation. For the 150 ALA biospecimens with values below the laboratory limit of detection (0.97 ng/mL), we assigned a value of 0.5, chosen as an approximate midpoint between zero and 0.97 ng/mL, on the assumption that ALA was present in samples but only at very low levels. This produced a dataset for this analysis of 605 participants with no missing values.

Statistical analyses were conducted in Stata/SE 14.2 (Stata Corporation, College Station, TX). Our assessment showed that, like many other biological measures with a true zero value, distributions of PUFAs were positively skewed, and log (and other) transformations fail to produce a Gaussian distribution. When the sample is larger than 100 observations the non-normal distribution is not a threat because under central limit theorem the distribution of sample means approximates a normal distribution, regardless of the population distribution. Interestingly, the long-chain PUFAs ratio (our main independent variable) more closely approximated a normal distribution than the individual PUFAs themselves. Distributions of PUFAs were assessed for normality using the Shapiro-Wilk test, and given the large sample size, were analyzed using parametric tests. Pearson correlation tested the strength of relationship between the pain intensity values. We plotted histograms of pain intensity variables (Supplementary Figure 1) and the n-6/n-3 PUFA ratio (Supplementary Figure 2).

Preliminary analysis compared the distribution of mean pain intensity scores for each pain condition according to participant demographic and behavioral characteristics to assess for potential confounding. For each pain condition, we graphed the proportions of participants who were cases, symptomatic non-cases, and non-cases without pain to visualize these distributions.

We conducted a series of five multiple linear regression models, in which one of the five continuous pain intensity scores was the dependent variable. The main exposure in each model was the n-6/n-3 PUFA ratio calculated as n-6 AA divided by the sum of n-3 DHA and

n-3 EPA. Covariates comprised the z-score standardized measures of the precursor PUFAs n-6 LA and n-3 ALA, OPPERA study site, and participant characteristics of age, sex, race/ethnicity, body mass index and smoking status. When the addition of a demographic or behavioral covariate to the linear regression model changed the measure of association by ≥10%, we took this as likely evidence of confounding and included the variable in the model. These analyses tested the hypothesis that a higher n-6/n-3 PUFA ratio was associated with greater pain intensity. The beta coefficients and their 95% confidence intervals from these models were depicted in forest plots and interpreted as the change in pain intensity per unit increase in the n-6/n-3 PUFA ratio. Confidence intervals that did not overlap the null value of zero, are interpreted as statistically significant. Values on the right side of zero indicate that pain intensity increases as the n-6/n-3 PUFA ratio increases.

The next series of five multiple linear regression analyses retained the same dependent variables and covariates but replaced the n-6/n-3 PUFA ratio with concentrations of individual PUFAs that were standardized to z-scores. This allowed a comparison of the relative magnitude of the effects of a one standard deviation change in the independent variable on the pain intensity outcome of interest. These results were tabulated.

Statistical power was calculated for the fixed sample size of 605 OPPERA-II participants with stored blood samples and non-missing values for the variables analyzed in this paper. Using the SAS v9.4 power procedure for linear regressiontests of the association between PUFA ratio and orofacial pain intensity and specifying power of 0.80 and type I error of 0.05, we determined that the minimum detectable regression coefficient was 5.4 (i.e., a change of 5.4 units in pain intensity associated with a 1.0 unit change in PUFA ratio).

RESULTS

Sample description

Of the 605 study participants, approximately two thirds either met case classification for orofacial pain, headache, and bodily pain, or reported sub-clinical pain symptoms typical of those conditions (Figure 1). The numbers of cases and symptomatic non-cases were approximately equal for orofacial pain, headache, low back pain and abdominal pain. For low back pain and abdominal pain, approximately half the sample either met case classification or had pain symptoms typical of low back pain or irritable bowel syndrome. The intensity levels of present pain, worst pain and average pain were most weakly correlated for abdominal pain condition, where the strength of association between present and average pain was r=0.316] and most strongly correlated for orofacial pain, where the strength of association between worst and average pain was r=0.770]. Pairwise correlation between pain intensity values ranged from a moderately strong relationship for bodily and abdominal pain intensity (r =0.31) to a strong relationship for orofacial and headache pain intensity (r =0.71). These results are reported in Supplementary Table 3.

Descriptive statistics

In unadjusted analysis (Table 1), TMD cases and low back pain cases had a significantly higher mean n-6/n-3 PUFA ratio than the pain-free non-case referents. Although mean

n-6/n-3 PUFA ratios did not differ significantly across categories of the other pain conditions, n-6/n-3 PUFA ratio values were highest in cases and lowest in pain-free non-cases for all five pain conditions. A comparison of unadjusted mean pain intensity ratings (Table 1) showed that the mean pain intensity of cases ranged from 33.7 for irritable bowel syndrome to 61.1 for fibromyalgia. Within each pain condition, cases had significantly greater pain intensity than symptomatic non-cases.

Women reported greater pain intensity than men, on average, for all pain conditions except low back pain for which sex differences were non-significant (Table 2). Pain intensity did not vary according to age group or race/ethnicity for any condition. People with low back pain, abdominal pain and bodily pain who were obese reported greater pain intensity than people with these pain conditions whose body mass index was lower. Current smokers reported greater pain intensity than non-smokers for all pain conditions except abdominal pain where differences did not differ by smoking status.

Relationship between n-6/n-3 PUFA ratio and pain intensity

The main result for this study is reported in the forest plots (Figure 2) taken from five separate multiple linear regression models. After adjustment for potential confounding of OPPERA study site, and participant characteristics of age, sex, race/ethnicity, body mass index and smoking status and the precursor PUFAs n-6 LA and n-3 ALA, orofacial pain intensity increased 5.7 points (95% CI: 1.4, 9.9) per unit increase in n-6/n-3 PUFA ratio. A similar magnitude of effect was observed for the intensity of headache pain, which increased significantly by 5.0 points (95% CI: 0.9, 9.2) per unit increase in n-6/n3 PUFA ratio. Likewise bodily pain intensity increased by a similar magnitude (5.3 points, 95% CI: 0.4, 10.2) per unit increase in n-6/n-3 PUFA ratio, while low back pain intensity increased by 8.4 points (95% CI: 3.8, 13.0). Only the association of n-6/n3 PUFA ratio and abdominal pain intensity was null. The full models are reported in Supplementary Tables 4–8.

To understand which constituent of the n-6/n-3 PUFA ratio contributed most strongly to associations with pain intensity, we disaggregated the ratio into its individual components, standardized them for direct comparison, and reported results in Tables 3 to 7. Most notably, n-3 DHA was inversely and significantly associated with lower intensity of both orofacial pain (Table 3) and headache pain (Table 4). DHA did not make the sole contribution. The n-6 AA was associated with greater intensity of low back pain (Table 5) and n-3 EPA association with lower intensity of low back pain (Table 5) was of borderline significance. Although the two precursors of long-chain PUFAs were not included in the PUFA ratio, these analyses showed that the associations of n-6 LA with greater pain intensity of orofacial pain (Table 3) and greater intensity of abdominal pain (Table 6) were of borderline statistical significance. The n-3 ALA was not associated with the pain intensity of any condition.

DISCUSSION AND CONCLUSIONS

In this community-based study, a higher n-6/n-3 long-chain PUFA ratio was associated with greater intensity of orofacial pain, headache, low back pain, and bodily pain in analysis adjusted for confounding pain intensity increased between 5 and 8 points, on average, on a

0–100 scale for each unit increase in the n-6/n-3 PUFA ratio. Only abdominal pain was not associated with the n-6/n-3 PUFA ratio.

Approximately half of the participants reporting pain were symptomatic non-cases, shedding light on the relationship between PUFAs and pain intensity in this understudied sub-clinical population. Symptomatic non-cases reported lower pain intensity for all five pain conditions than did cases, yet symptomatic non-cases are potentially at risk of transitioning to pain case status. Although differences did not reach the threshold for statistical significance, estimates of the n-6/n-3 PUFA ratio for symptomatic cases was higher than for non-cases, and lower than for pain cases. When the PUFA ratio was disaggregated into its long-chain fatty acid constituents, the n-3 DHA was more strongly associated with pain intensity than other constituents, being inversely and significantly associated with orofacial pain and headache, and of borderline significance with bodily pain. Of note however, the n-6/n-3 PUFA ratio had a more consistent association the intensity of pain than had any single fatty acid.

The n-6/n-3 PUFA ratio effect estimate was close to zero for abdominal pain intensity, unlike the four other types of pain where effect estimates ranged from 5 to 8. Relative to the mean pain ratings for those four pain conditions, the effect estimates represent increases ranging from 16% (headache) to 38% (low back pain). In terms of clinical significance, those relative differences range from minimally-important to moderately-important using benchmarks for interpreting results from clinical trials of chronic pain.[12]

One explanation for the smaller effect estimate seen for IBS is the low pain intensity rating for abdominal pain. The mean abdominal pain intensity rating of irritable bowel syndrome cases was 33.7. This is at least 10 points lower than average pain intensity ratings of temporomandibular disorder and headache cases, more than 20 points lower than pain intensity ratings of low back pain cases, and almost 30 points lower than pain intensity ratings of fibromyalgia cases. From a statistical perspective, the low pain intensity rating has limited variability, making it more difficult to detect a significant association if one is present. By way of comparison, the mean abdominal pain intensity rating was 4.5 on a 0–10 numeric rating scale for 257 Rome III irritable bowel syndrome patients in the IBS PROOF cohort.[44] This is equivalent to 45 on a 0–100 scale, and approximately 25% higher than the pain rating of our cases. A difference in pain intensity of that magnitude is reasonable considering the PROOF cohort was drawn from a patient registry whereas our sample was drawn from the community.

Despite the null association between the n-6/n-3 PUFA ratio and abdominal pain intensity, it remains possible that PUFAs influence abdominal pain indirectly through their effect on psychologic distress, as this is an established risk factor for development of irritable bowel syndrome.[26] We showed in an earlier analysis of this study population that a higher n-6/n-3 PUFA ratio was associated with two markers of psychological distress associated with irritable bowel syndrome: somatic symptom disturbance and depressive symptoms.[36] Supporting the possibility of a mediating role of psychological stress, Alfven and Strandvik[1] reported that, compared with healthy controls, children with psychosomatic recurrent abdominal pain had lower circulating levels of n-3 PUFAs, resulting in a higher ratio n-6 LA to n-3 ALA and a higher ratio n-6 AA to n-3 EPA.

Of the individual constituents of the n-6/n-3 PUFA ratio, the n-3 DHA was more strongly associated with pain intensity than either n-6 AA or n-3 EPA. DHA is the long-chain elongation and desaturated product of the n-3 ALA, and a biosynthetic precursor of novel classes of specialized pro-resolving mediators (SPMs) including the D-series resolvins (RvD1, RvD2, RvD3, RvD4, and RvD5), maresins, and protectins. In their mouse model of tibial bone fracture, Zhang et al.,[51] showed that RvD1, RvD5, and neuroprotectin D1 had potent analgesic effects when administered post-operatively. Moreover, when delivered perioperatively, DHA, RvD1 and maresin-1 prevented or delayed onset of post-operative pain. Zhang et al.,[51] observed that SPMs were active in the nanogram range to achieve analgesic effects. In comparison, 1000 times higher amounts of DHA were required to achieve the same effects.[51] In other preclinical rodent studies of chronic inflammatory pain, SPMs derived from n-3 EPA or DHA were shown to reduce heat hyperalgesia[28, 50] and mechanical hyperalgesia.[49]

Although our LC-MS/MS analysis was unable to quantify the potent DHA-derived oxylipins such as the D-series resolvins in sufficient numbers for analysis, it is reasonable to infer that DHA is a proxy measure for these derivatives. Support for this inference comes from an RCT conducted by Ramsden et al.,[31] that assessed the clinical biochemical effects of targeted alteration in dietary PUFAs in adults with chronic headache. These investigators found that higher circulating levels of DHA produced marked increases in its antinociceptive n-3 pathway markers 18-hydroxy-eicosapentaenoic acid and 17-hydroxy-docosahexaenoic acid that are direct metabolic intermediates for E- and D-series resolvins, maresins, prostaglandins, endovanilloids, and endocannabinoids.

Goldberg and Katz[16] produced strong supporting evidence for an inverse relationship between n-3 PUFAs and pain intensity in human subjects. They conducted a meta-analysis of 13 randomized controlled trials (RCTs) that evaluated the analgesic efficacy of dietary supplementation of long-chain n-3 PUFAs versus placebo for 3–4 months in 501 adults with rheumatoid arthritis or joint pain secondary to inflammatory bowel disease and dysmenorrhea. Compared to placebo, n-3 PUFAs achieved greater reduction in patient reported joint pain intensity (SMD: −0.26; 95% confidence interval *CI+: −0.49 to −0.03, p=0.03).[16] More recently, an RCT assigned 182 adults with chronic migraine to one of three dietary interventions for 16 weeks: a diet that increased intake of omega-3 (n-3) PUFAs; a diet that increased n-3 PUFAs and concurrently decreased omega-6 (n-6) PUFA intake; or a controlled diet that maintained U.S. average intakes of n-3 and n-6 PUFAs. At 16 weeks, both interventions that increased n-3 PUFA intake achieved greater reductions in headache severity and in headache-related drugs or NSAIDS use than the control diet.[32]

Our findings build on evidence from these RCTs. Although the cross-sectional design of our study precludes causal inference, we draw attention to the n-6/n-3 PUFA imbalance as a possible risk factor for greater pain intensity. For ethical reasons, RCTs do not administer n-6 enriched diets because of the risk for exacerbating pain, so most RCT examine only the protective effects of n-3 PUFAs. Yet from animal studies we see that dietary n-6 LA and AA are precursors of pronociceptive oxylipins.[15, 39] In their rodent model, Boyd et al.,[7] demonstrated that rats fed a n-6 PUFA enriched diet evoked nociceptive hypersensitivity to noxious stimuli, onset of peripheral nerve damage, and pain-related behaviors within 8

weeks. When the diet was subsequently reversed to being enriched in n-3 PUFAs, these symptoms resolved. Because our study examined the balance between n-6 and n-3 PUFAs, findings add new knowledge that an imbalanced PUFA ratio favoring n-6 PUFAs matters more for pain intensity than the absolute levels of the individual PUFAs.

Interest in the health effects of PUFAs has focused primarily on inflammatory diseases such as cardiovascular diseases and depression, finding that n-3 PUFAs decrease expression of inflammatory genes,[33] and increase secretion of EPA- and DHA-derived SPMs that act to inhibit pro-inflammatory signaling.[38] The Emerging interest in pain has tended to follow that paradigm by studying pain syndromes with an inflammatory component, such as rheumatoid arthritis and dysmenorrhea.[16] Our study differs from that paradigm because orofacial pain, headache, low back pain, abdominal pain and bodily pain show little peripheral inflammatory pathology.[48] The implications of our findings, then, are that a low n-6/n-3 PUFA ratio may reduce pain intensity through mechanisms other than their effects on inflammation.

Strengths of this study include the parent OPPERA-II study's content expertise, study population, rigor in measuring pain and its collection of biospecimens. We quantified circulating PUFAs with liquid chromatography tandem mass spectrometry that quantifies both exogenous and endogenous sources of PUFAs. We quantified PUFAs in circulating erythrocytes. The parent study OPPERA-II did not conduct a food frequency questionnaire (FFQ) to assess dietary intake of PUFAs and did not assess use of dietary supplements. Therefore, we are unable to determine the correlation between circulating levels of PUFAS and dietary intake. Since circulating PUFA concentrations take account of variability in metabolism and absorption, they more accurately assess bioavailability than dietary intake measures. Unlike plasma, PUFAs measured in erythrocytes are insensitive to fasting status and reflect dietary PUFA intake over the preceding 120 days.[4, 8] Of the limitations, our analysis was restricted to the n-3 and n-6 precursor PUFAs, rather than their oxylipins derivatives. We were unable to quantify in a sufficient number of samples oxidized derivatives of n-6 LA including epoxyoctadecaenoic acid (EpOMEs) and hydroxyoctadecadienoic acids (HODEs) or oxidized derivatives from n-6 AA such as prostanoids, epoxyeicosatrienoic acids (EETs) and mid-chain hydroxyeicosatetraenoic acids (HETEs). Neither were we able to quantify the SPM intermediate 17-hydroxydocosahexaenoic acid (17-HDHA) or the EPA-metabolite 18-hydroxyeicosapentaenoic acid (18-HEPE) from most samples.

In the absence of fasting blood, we measured PUFA concentrations in red blood cells, rather than in plasma. Unlike plasma, PUFAs measured in erythrocytes are insensitive to fasting status and reflect dietary PUFA intake over the preceding 120 days.[4, 8]

In this study, 33.1% of participants had none of the assessed pain conditions and 29.3% had one pain condition only. The remaining 37.7% had at least two pain conditions. When interpreting associations between the PUFA ratio and any single pain condition, it is important to consider that the presence of one or more other pain conditions might be driving the association. This is not a limit of the study per se, as it simply reflects

circumstances in the general population in which chronic pain conditions tend to overlap in the same people.

For adults with persistent pain, the conventional treatment by pharmacologic management is limited by incomplete and short-acting relief, analgesic tolerance, adverse side-effects and risk of addiction.[22, 25, 29] As power was inadequate to test whether the association was stronger in pain cases than in symptomatic non-cases, interaction analyses were not conducted. Nonetheless, the findings of this study raise the possibility that for symptomatic non-cases, in whom pain intensity was lower than for cases, dietary changes or supplements that redress the n-6/n-3 PUFA ratio imbalance may present an acceptable alternative. Future studies can investigate how fatty acids may influence other characteristics of chronic pain, such as the frequency of pain episodes, the duration of pain and the extent of overlap with other pain conditions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Disclosures

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Highlights

- A higher n-6/n-3 long-chain PUFA ratio was associated with greater pain intensity
- This association found for orofacial, headache, low back and bodily pain intensity
- This association was found for symptomatic non-cases as well as cases
- n-6/n-3 ratio more consistently associated with pain intensity than single PUFAs
- Among the individual PUFAs, DHA was most strongly associated with pain intensity

Perspective

Perspective: A higher ratio of n-6/n-3 long-chain polyunsaturated fatty acids was associated greater pain intensity for orofacial pain, headache, low back pain, and bodily pain, but not abdominal pain. The n-6/n-3 PUFA ratio was more consistently associated with pain intensity than any individual constituent of the long-chain PUFA ratio.

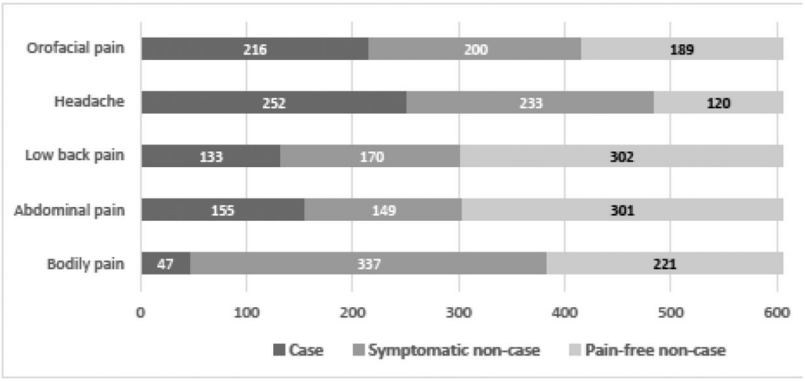

Figure 1.

Number of participants that met criteria for formal case classification (cases), sub-clinical symptoms of hallmark pain conditions (symptomatic non-cases); non-cases without pain (pain-free non-cases) for five chronic pain conditions.

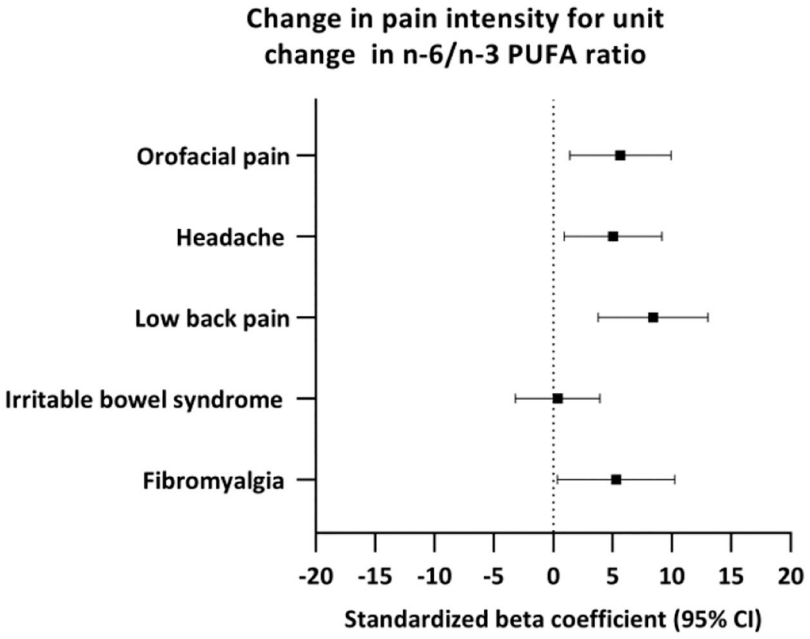

Figure 2.

Data points are the covariate-adjusted mean change in pain intensity per unit increase in n-6/n-3 PUFA ratio expressed as AA/(EPA+DHA). Three aspects of pain intensity were evaluated: Pain intensity computed as a 0–100 index based on pain ratings at: the present time; the worst pain; and the average pain over the prior three months. Pain intensity was rated separately for each of five pain conditions: orofacial pain, headache, low back pain, abdominal pain, and bodily pain. Standardized beta coefficients were estimated in a separate linear regression model for each pain condition where the dependent variable was the pain intensity score for the pain condition and n-6/n-3 PUFA ratio was the predictor variable. All models adjusted for n-6 linoleic acid, n-3 alpha-linolenic acid, OPPERA-II study site, and participant sex, age, race/ethnicity, body mass index and smoking status. Estimates that cross the null value of zero are not statistically significant.

Table 1.

Mean n-6/n-3 PUFA ratio and 95% confidence interval (CI) and mean pain intensity (95% CI) for cases, symptomatic non-cases and pain-free non-cases for each pain condition, (N=605)

	Mean n-6/n-3 PUFA ratio[a]	sd	95% CI	P	Mean pain intensity[b]	sd	95% CI	P
Orofacial pain								
Temporomandibular disorder case (n=216)	1.04	0.68	0.95, 1.13	0.042	43.3	19.69	40.7, 46.0	<0.001
Symptomatic non-case (n=196)	0.95	0.57	0.87, 1.03	0.657	31.2	16.70	28.8, 33.5	<0.001
Pain-free non-case (n=193)	0.92	0.51	0.85, 0.99	Ref	0.0			Ref
Headache pain								
Headache case (n=252)	0.99	0.63	0.91, 1.07	0.129	46.2	18.27	43.9, 48.5	<0.001
Symptomatic non-case (n=231)	1.00	0.56	0.93, 1.08	0.083	30.3	14.68	28.4, 32.2	<0.001
Pain-free non-case (n=122)	0.89	0.58	0.78, 0.99	Ref	0.0			Ref
Low back pain								
Low back pain case (n=133)	1.05	0.62	0.94, 1.16	0.028	55.0	18.93	51.7, 58.2	<0.001
Symptomatic non-case (n=169)	1.02	0.70	0.91, 1.12	0.068	32.3	17.15	29.7, 34.9	<0.001
Pain-free non-case (n=303)	0.91	0.52	0.86, 0.97	Ref	0.0			Ref
Abdominal pain								
Irritable bowel syndrome case (n=155)	1.03	0.71	0.92, 1.14	0.077	33.7	18.93	31.0, 36.5	<0.001
Symptomatic non-case (n=145)	1.00	0.55	0.91, 1.09	0.201	29.8	17.15	27.1, 32.5	<0.001
Pain-free non-case (n=305)	0.93	0.55	0.87, 0.99	Ref	0.0			Ref
Bodily pain								
Fibromyalgia case (n=47)	1.08	0.79	0.85, 1.30	0.100	61.1	14.06	57.1, 65.2	<0.001
Symptomatic non-case (n=337)	0.99	0.62	0.93, 1.06	0.139	45.8	19.22	43.7, 47.8	<0.001
Pain-free non-case (n=221)	0.92	0.50	0.85, 0.98	Ref	0.0			Ref

[a] The n-6/n-3 PUFA ratio was computed as AA/(EPA + DHA)

[b] Pain-free non-cases were assigned a score of zero for pain intensity

Ref refers to the referent category

Table 2.

Unadjusted associations of participant characteristics with pain intensity measured on a 0–100 scale for five pain conditions, (n=605 participants)

	N, %	Orofacial pain	Headache	Low back pain	Abdominal pain	Bodily pain
All participants	605, 100.0	25.6 (1.0)	30.8 (0.9)	21.1 (1.1)	15.8 (0.8)	30.2 (1.1)
Sex						
Men	202, 33.4	21.5 (1.6)	26.3 (1.6)	20.9 (1.8)	9.5 (1.2)	27.6 (2.0)
Women	403, 66.6	27.6 (1.2)	33.1 (1.1)	21.2 (1.3)	18.9 (1.0)	31.6 (1.4)
P-value		0.003	<0.001	0.873	<0.001	0.091
Age, y						
18–29	165, 27.3	26.1 (1.7)	30.6 (1.6)	18.9 (1.8)	18.0 (1.6)	26.9 (1.9)
30–39	169, 27.9	23.2 (1.7)	29.3 (1.7)	19.7 (1.9)	15.5 (1.5)	25.6 (2.1)
40–49	173, 28.6	26.3 (2.0)	32.9 (1.9)	23.9 (2.2)	15.6 (1.6)	34.6 (2.2)
50–74	98, 16.2	27.6 (2.5)	30.1 (2.5)	22.3 (2.8)	12.8 (1.8)	36.2 (3.0)
P-value		0.439	0.518	0.282	0.229	0.227
Race/ethnicity						
White	404, 66.8	25.8 (1.1)	31.0 (1.1)	21.5 (1.2)	14.9 (0.9)	29.5 (1.3)
African American	137, 22.6	22.5 (2.1)	28.0 (2.1)	20.9 (2.5)	16.8 (2.0)	30.5 (2.6)
Asian	20, 3.3	23.0 (5.1)	29.3 (5.7)	10.3 (4.2)	13.8 (3.5)	24.3 (5.4)
Hispanic	32, 5.3	36.0 (5.5)	39.9 (4.4)	23.8 (5.3)	21.5 (4.5)	38.1 (5.4)
Other	12, 2.0	30.3 (5.7)	33.9 (6.8)	22.8 (7.7)	22.5 (6.0)	41.4 (8.0)
P-value		0.054	0.108	0.416	0.258	0.217
Body mass index						
Normal weight	239, 39.5	24.1 (1.4)	30.3 (1.4)	18.9 (1.6)	17.2 (1.2)	27.8 (1.7)
Overweight	172, 28.4	23.9 (1.7)	28.7 (1.7)	18.4 (1.8)	12.5 (1.5)	26.5 (2.0)
Obese	194, 32.1	28.9 (1.9)	33.4 (1.8)	26.2 (2.1)	16.9 (1.5)	36.5 (2.2)
P-value		0.064	0.131	0.004	0.011	0.024
Smoking status						
Lifetime non-smoker	425, 70.3	23.6 (1.1)	29.6 (1.1)	19.0 (1.2)	15.9 (0.9)	26.9 (1.3)
Former	94, 15.5	29.0 (2.5)	33.0 (2.4)	27.8 (2.8)	16.0 (2.0)	37.3 (2.8)
Current	86, 14.2	31.5 (2.8)	34.5 (2.8)	24.4 (3.3)	15.0 (2.5)	39.0 (3.3)
P-value		0.006	0.007	0.017	0.926	0.035

Values are mean (standard error) from a simple linear regression model

Table 3.

Adjusted[a] beta coefficients and 95% confidence limits (CL) for association between standardized PUFA concentration and intensity of orofacial pain

Orofacial pain intensity	Beta	95% CL	P-value
Linoleic acid z-score	4.5	−0.3, 9.3	0.067
Arachidonic acid z-score	1.2	−1.7, 4.1	0.415
Alpha-linolenic acid z-score	0.1	−4.2, 4.4	0.959
Eicosapentaenoic acid z-score	1.6	−8.2, 11.4	0.742
Docosahexaenoic acid z-score	−36.7	−61.9, −11.6	0.004

[a]Multiple linear regression model additionally adjusts for OPPERA study site, and participant age, sex, race/ethnicity, body mass index and smoking status

Table 4.

Adjusted[a] beta coefficients and 95% confidence limits (CL) for association between standardized PUFA concentration and intensity of headache pain

Headache pain intensity	Beta	95% CL	P-value
Linoleic acid z-score	3.1	−1.6, 7.8	0.191
Arachidonic acid z-score	1.6	−1.2, 4.4	0.260
Alpha-linolenic acid z-score	−0.8	−5.0, 3.4	0.700
Eicosapentaenoic acid z-score	−1.0	−10.5, 8.5	0.836
Docosahexaenoic acid z-score	−25.7	−50.0, −1.4	0.038

[a]Multiple linear regression model additionally adjusts for OPPERA study site, and participant age, sex, race/ethnicity, body mass index and smoking status

Table 5.

Adjusted[a] beta coefficients and 95% confidence limits (CL) for association between standardized PUFA concentration and pain intensity from low back pain

Low back pain intensity	Beta	95% CL	P-value
Linoleic acid z-score	0.0	−5.4, 5.3	0.995
Arachidonic acid z-score	3.3	0.1, 6.5	0.045
Alpha-linolenic acid z-score	2.7	−2.1, 7.5	0.270
Eicosapentaenoic acid z-score	−10.3	−21.1, 0.6	0.064
Docosahexaenoic acid z-score	−13.8	−41.7, 14.1	0.333

[a]Multiple linear regression model additionally adjusts for OPPERA study site, and participant age, sex, race/ethnicity, body mass index and smoking status

Table 6.

Adjusted[a] beta coefficients and 95% confidence limits (CL) for association between standardized PUFA concentration and abdominal pain intensity

Abdominal pain intensity	Beta	95% CL	P-value
Linoleic acid z-score	4.0	0.0, 8.1	0.052
Arachidonic acid z-score	−1.2	−3.6, 1.2	0.333
Alpha-linolenic acid z-score	−1.9	−5.5, 1.7	0.299
Eicosapentaenoic acid z-score	1.8	−6.4, 10.0	0.662
Docosahexaenoic acid z-score	−7.4	−28.4, 13.7	0.492

[a]Multiple linear regression model additionally adjusts for OPPERA study site, and participant age, sex, race/ethnicity, body mass index and smoking status

Table 7.

Adjusted[a] beta coefficients and 95% confidence limits (CL) for association between standardized PUFA concentration and bodily pain intensity

Bodily pain intensity	Beta	95% CL	P-value
Linoleic acid z-score	4.0	−1.7, 9.7	0.165
Arachidonic acid z-score	1.6	−1.8, 4.9	0.365
Alpha-linolenic acid z-score	−0.2	−5.3, 4.9	0.946
Eicosapentaenoic acid z-score	−2.1	−13.7, 9.4	0.718
Docosahexaenoic acid z-score	−26.2	−55.8, 3.3	0.082

[a]Multiple linear regression model additionally adjusts for OPPERA study site, and participant age, sex, race/ethnicity, body mass index and smoking status