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Original article

Fish consumption, omega-3 fatty acid intake, and risk of pain: the Seniors-ENRICA-1 cohort

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SUMMARY

Background & aims: Omega-3 fatty acids have anti-inflammatory and analgesic (anti-nociceptive) actions. However, the relation of habitual omega-3 fatty acid intake and fish consumption - its main food source - with pain remains largely unknown. We examined the association of fish consumption and marine omega-3 fatty acid intake with pain incidence and worsening over 5 years among older adults.

Methods: Data were taken from the Seniors - ENRICA-1 cohort, which included 950 individuals aged ≥60 years in Spain. Habitual fish consumption and marine omega-3 fatty acid intake during the previous year were assessed in 2008–2010 and 2012 with a validated diet history. Pain was assessed in 2012 and 2017 with a scale developed from the Survey on Chronic Pain in Europe, ranging from 0 (no pain) to 6 (highest pain), according to its severity, frequency, and number of locations. Analyses on pain incidence were conducted in the 524 participants free of pain at baseline, while those on pain worsening were performed in the overall cohort, and both were adjusted for sociodemographic variables, lifestyle, morbidity, and diet quality.

Results: Higher oily fish consumption was associated with reduced pain incidence and worsening over 5 years [fully adjusted odds ratios (95% confidence interval) = 0.68 (0.50,0.94) and 0.70 (0.55,0.88) for every 25 g/day increment (1.5 servings/week), respectively]. Total and white fish consumption were not associated with pain. Higher marine omega-3 fatty acid intake was inversely associated with pain worsening [odds ratio (95% confidence interval) per 0.5 g/day increment = 0.83 (0.72,0.96)]. The corresponding associations for eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) were 0.53 (0.33,0.87) and 0.73 (0.57,0.94).

Conclusions: In this cohort of Spanish older adults, increased oily fish consumption was inversely associated with pain incidence and worsening over 5 years, while higher marine omega-3 fatty acid intake (and that of EPA and DHA) was linked to less pain worsening.

1. Introduction

1.1. Background and rationale

Chronic pain is a common symptom that affects 25–35% of adults and up to 60% of people older than 65 years worldwide [1–4]. Chronic pain prevalence has risen over the last few decades and this trend is expected to continue due to the progressive aging of the global population [5]. Namely, years lived with disability caused by musculoskeletal disorders were 20% higher in 2016 than in 2006 [6], while 5 of the top 10 diseases responsible for most of the years lived with disability are pain-driven conditions [7]. As a result, there is a

Abbreviations: BMI, Body mass index; CI, Confidence interval; DHA, Docosahexaenoic acid; EPA, Eicosapentaenoic acid; NSAID, Nonsteroidal anti-inflammatory drug; OR, Odds ratio.

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heavy, partly elderly - driven, burden of healthcare usage, disability, and lost productivity – note that individuals with moderate - to - severe chronic pain lose 8 days of work every 6 months, on average [7].

The need to prevent and minimize said burden has spurred the quest for novel and effective response strategies [5,8]. On one hand, more evidence on chronic pain prevention is needed, as there is little evidence on what interventions do and do not work - except for physical exercise [8]. On the other hand, first-line chronic pain management should rely on non-pharmacological interventions, but their effectiveness is modest and are supported by limited evidence [8]. Moreover, painkiller use in older adults may be hampered by polypharmacy, excess toxicity, tolerance, dependance, and risks on cognition and organ systems [9,10].

A growing number of biological mechanisms support foods and nutrients as potential means to prevent and reduce chronic pain [11,12]. Because of their anti-inflammatory, pro-resolving, and analgesic (anti-nociceptive) actions, omega-3 fatty acids and fish – being their main food source – may play a role in chronic pain prevention and management [12–14]. Indeed, there is some evidence from intervention studies that omega-3 fatty acid supplements may reduce general musculoskeletal pain, exercise-induced pain, osteoarthritic pain, and dysmenorrhea (i.e., painful menstrual cramps) [15,16]. Among patients with rheumatoid arthritis, this supplementation might lower pain intensity and possibly lead to reduced or delayed use of anti-inflammatory drugs [13,17,18]. Besides, observational studies among these patients have found that fish consumption and omega-3 fatty acid intake are associated with a decreased risk for rheumatoid arthritis, lower odds of high pain intensity/refractory pain, and reduced disease activity [19–21], whereas serum levels of omega-3 fatty acids are inversely associated with rheumatoid arthritis-progression biomarkers and osteoarthritis knee pain symptoms [19,22]. Omega-3 fatty acids -either directly or via substitution for omega-6 fatty acids-may also reduce the omega-6:omega-3 ratio, which may be upregulated in rheumatoid arthritis and has been associated with more knee pain symptoms in patients with osteoarthritis [22,23].

However, the role of fish consumption and omega-3 fatty acid intake as chronic pain prevention strategies remains largely unexamined. This approach may allow to compare whole-food and single nutrient associations, as fish is not only a source of omega-3 fatty acids, but also of vitamins, minerals, and amino acids, which may modulate inflammation and oxidative stress [14]. Another strength of whole-food analyses is that they resemble habitual clinical practice interventions that are achievable through changes in diet rather than additional supplements [11].

Moreover, existing trials on fish oil supplementation also have their limitations. First, they are heterogeneous, as they may include one or several omega-3 fatty acids [e.g., eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)] in different proportion [13,24]. Second, some of these trials use placebo sources that might have anti-inflammatory actions themselves, such as olive oil or corn oil [13,24]. Third, most focus on rather short-term interventions (i.e., 3–12 months), which are unlikely to capture potential effects on the underlying conditions causing chronic pain, likely requiring long-term supplementation to become evident [13,24]. Fourth, there might be no additional pain benefits of very high omega-3 fatty acid dosing, and its safety is not yet fully understood [14,17,25].

1.2. Objectives

We accordingly examined the association of fish consumption and marine omega-3 fatty acid intake with pain incidence and pain worsening over 5 years in a cohort of community-dwelling older adults. We delved deeper into these associations by examining the main fish types (white and oily), omega-3 fatty acids (EPA and DHA), and pain components (severity, frequency, and number of locations) separately [2,26].

2. Methods

2.1. Study design and participants

We used data from the Seniors-ENRICA-1 study (ClinicalTrials.gov Identifier: NCT01133093), a cohort of community-dwelling individuals aged 60 years and older in Spain. Participants were recruited from March 2008 to September 2010 and followed-up in 2012 (February to November) and 2017 (January to July) [27,28]. We studied whether the average fish consumption and marine omega-3 fatty acid intake between 2008–2010 and 2012 were associated with pain incidence and pain worsening from 2012 to 2017.

In all data collection waves, information on pain, sociodemographic, lifestyle, and morbidity variables was gathered through computer-assisted telephone interviews, while trained personnel conducted home-based electronic validated diet histories (to assess food consumption) and a set of physical examinations (including weight and height measurements and blood draws) [27,28]. The Clinical Research Ethics Committee of the "La Paz" University Hospital in Madrid approved the research protocol, and all subjects gave written informed consent.

2.2. Variables

2.2.1. Fish consumption and omega-3 fatty acid intake

In 2008–2010 and 2012, we assessed food consumption with a validated, face-to-face, electronic diet history [27,29], in which subjects could report 860 foods and recipes habitually consumed during the previous year, with the help of 127 digitized photographs and household measures to estimate food portion sizes (Supplementary Appendix 1). To convert foods to nutrients (including omega-3 fatty acids, EPA, and DHA), the electronic diet history used data from six food composition tables from Spain and five tables from other countries [29]. This diet history was validated against seven 24-h recalls over one year, and the mean correlation coefficients were 0.42 for fish consumption, 0.55 for EPA, 0.60 for DHA, and 0.76 for energy [29].

To minimize measurement error in fish consumption and marine omega-3 fatty acid intake, we averaged the 2008–2010 and 2012 data. According to their fat content, fish species were grouped into white (e.g., cod, grouper, hake, halibut, pollock, sea bass, sea bream, sole, turbot, whiting), oily (e.g., anchovies, herring, mackerel, salmon, sardines, swordfish, trout, tuna), and other (i.e., lacking information, thus not examined as an independent variable in the analyses).

We also grouped the total intake of marine omega-3 fatty acids (i.e., EPA, DHA, docosapentaenoic acid, α-linolenic acid, and stearidonic acid coming from fish and seafood, leaving out those from other dietary sources). EPA and DHA were further examined as independent variables in the analyses (note that the intake of the other fatty acids was sparing). We did not examine omega-3 intake via supplements (reported by 0.53% of the study subjects), as we lacked any dosing data.

2.2.2. Pain

We assessed self-reported pain in the preceding six months with six questions from the Survey on Chronic Pain in Europe (see Supplementary Appendix 2) [2]. We then developed a pain scale that consisted of three components [26]: (1) pain frequency, grouped into sporadic (weekly or less, scored 1 point) or persistent

pain (at least 2 times/week, scored 2 points); (2) pain severity, grouped into light (troubling a little or nothing on activities of daily living, scored 1 point) or moderate-to-severe (troubling moderately or more, scored 2 points); and (3) number of pain locations (head and neck, back, bones and joints, arms, legs, and other sites -abdomen, chest, or any other site), further grouped into 1–2 pain sites (scored 1 point) or ≥3 pain sites (scored 2 points). The scorings of the three components were then summed, so that the pain scale ranged from 0 (no pain) to 6 (highest pain). Finally, we defined incident pain as the presence of pain in 2017 among the subjects who had scored 0 points in the pain scale in 2012, and pain worsening as any increase in the pain scale between 2012 and 2017.

2.2.3. Other variables

We considered four sets of possible confounders of the study associations. Regarding sociodemographic characteristics, we gathered data on sex, age, and self-reported educational level (primary or less, secondary, or university) [27]. We also considered lifestyle variables, namely self-reported tobacco smoking in 2012 (never, former, or current); self-reported alcohol consumption in 2012 (never, former, or current); average energy intake (kcal/day) between 2008–2010 and 2012, taken from the diet history; average recreational physical activity (Metabolic Equivalents of task-hours/week), estimated with the validated EPIC-cohort questionnaire [30]; average time spent watching television (hours/day), assessed with the Nurses' Health Study questionnaire [31]; and average body mass index (BMI), calculated as weight (kg) divided by height (m) squared, both measured under standardized conditions [32]. We operationalized morbidity as the average number of chronic diseases between 2008 and 2010 and 2012. We considered diabetes -either treatment with antidiabetic drugs, blood glucose levels ≥126 mg/dL, or self-reported diabetes – and self-reported physician-diagnosed cardiovascular disease (coronary heart disease, stroke, or heart failure), chronic obstructive pulmonary disease, musculoskeletal disease (osteoarthritis, arthritis, or hip fracture), cancer, and depression (requiring medical treatment) [27]. Finally, we computed the Mediterranean Diet Score to account for diet quality, using diet history data on the average consumption of vegetables, legumes, fruit and nuts, cereals, meat and dairy, as well as the average intake of alcohol, monounsaturated fatty acids, and saturated fatty acids between 2008 and 2010 and 2012 [33].

For the interaction and sensitivity analyses, we also used data on the average omega-6 fatty acid intake (linoleic and arachidonic fatty acids) in 2008–2010 and 2012, and the frailty phenotype in 2012 (exhaustion, low physical activity, slow gait speed, unintentional weight loss, and muscle weakness). Subjects meeting 1–2 Fried criteria were considered pre-frail, whereas those with ≥3 criteria were deemed to be frail [34].

2.3. Statistical methods

2.3.1. Study size

From the 2519 participants evaluated in 2012, 196 (7.8%) had died and 1185 (47.0%) were lost to follow-up in 2017. From the remaining 1138 participants, we further excluded 188 (7.5%) with inadequate data (92 subjects had no information on diet, and 95 on pain, and 1 on potential confounders). Hence, the analytical sample for pain worsening comprised 950 individuals. For the analyses regarding pain incidence, we further excluded 426 subjects who already had pain in 2012 (scored >0 points in the pain scale). Therefore, this second analytical sample comprised 524 subjects (Supplementary Fig. 1). Characteristics of these participants, those with pre-existing pain in 2012, those who were not followed in 2017, and those with inadequate data are shown in Supplementary Table 1.

2.3.2. Statistical analyses

The associations of fish consumption and marine omega-3 fatty acid intake with pain incidence and pain worsening over 5 years (as well as those with the three pain components) were summarized with odds ratios (OR) and their 95% confidence interval (CI), obtained from logistic regression models. To assess dose–response relationships, fish consumption and marine omega-3 fatty acid intake were modeled in the analyses as (1) continuous variables [per 25 g/day and 0.5 g/day, respectively – roughly 1 standard deviation increments]; (2) categorical variables (quartiles, using the lowest as reference); and (3) restricted cubic splines (knots located at the 10th, 50th, and 90th percentiles [35]). Further details on variable categorization are shown in the corresponding tables and figures. We used two *a priori* incrementally adjusted models to control for potential confounding: the first, adjusted for sociodemographic variables, and the second, additionally adjusted for lifestyle, morbidity, and diet quality.

2.3.3. Interactions and sensitivity analyses

We also examined if the sociodemographic variables, frailty, lifestyle, morbidity, diet quality, and omega-6 intake modified the main study associations by using Wald tests that compared models with and without interaction terms, defined as the product of said variables by the continuous fish consumption or omega-3 fatty acid intake variables.

In addition, we conducted six sensitivity analyses. To check the robustness of the pain incidence and pain worsening associations, we further categorized incident pain into intermediate pain (3 or 4 points in the pain scale) and highest pain (5 or 6 points), and switched from our scale -developed from the Survey on Chronic Pain in Europe-to a standard Numeric Rating Scale for pain intensity, ranging from 1 (no pain at all) to 10 (the worst pain imaginable) (Supplementary Appendix 2) [2]. To prevent residual confounding, we adjusted the analyses for individual chronic diseases. Given that some mechanisms of action of nonsteroidal anti-inflammatory drugs (NSAIDs) may overlap with those of fish consumption and marine omega-3 fatty acid intake, we conducted additional analyses with adjustment for NSAID use in 2012 (checked by study staff against drug packages at home [27]). Because cancer pain and other pain types may not have overlapping mechanisms and management strategies, we excluded subjects with cancer history in 2012. Finally, given that dietary reference values for omega-3 fatty acid intake have been set [36] and that the balance between omega-6 and omega-3 fatty acids may be relevant to pain beyond their individual intakes [20,24], we used a cut-off point of ≥0.25 g/day for marine omega-3 fatty acid intake and examined whether the omega-6: omega-3 ratio was associated to pain incidence and worsening.

Analyses were performed with the Stata 15 software (Stata Corp. 2017. Stata Statistical Software: Release 15. College Station, TX, USA: Stata Corp LP).

3. Results

3.1. Descriptive data

The mean (standard deviation) absolute fish consumption was 71.6 (38.5) g/day, of which 37.1 (26.3) g/day were white fish and 25.8 (22.6) g/day oily fish. Means (standard deviations) for marine omega-3 fatty acid, EPA, and DHA intake were 0.91 (0.70) g/day, 0.26 (0.20) g/day, and 0.50 (0.40) g/day. Table 1 shows the characteristics of the study participants by quartiles of total fish consumption. Those who ate more fish were younger, more often men and less often never smokers and never drinkers, engaged in more physical activity and had higher energy intake and diet quality.

Table 1
Baseline characteristics of 524 older adults without pain and 950 older adults with and without pain, by quartiles of total fish consumption.

	Total fish consumption[a] (subjects without pain)				Total fish consumption[b] (subjects with and without pain)			
	Quartile 1[a]	Quartile 2[a]	Quartile 3[a]	Quartile 4[a]	Quartile 1[b]	Quartile 2[b]	Quartile 3[b]	Quartile 4[b]
n	131	131	131	131	238	237	238	237
Sex-Men, n (%)	59 (45.0)	66 (50.4)	86 (65.6)	87 (66.4)*	84 (35.3)	104 (43.9)	126 (52.9)	146 (61.6)*
Age (years)	71.4 (6.23)	71.7 (5.60)	69.9 (4.86)	70.7 (4.93)*	71.4 (5.70)	71.2 (5.47)	69.7 (4.72)	70.5 (5.06)*
Educational level, n (%)								
Primary or less	69 (52.7)	50 (38.2)	51 (38.9)	53 (40.5)	140 (58.8)	99 (41.8)	115 (48.3)	105 (44.3)*
Secondary	34 (26.0)	39 (29.8)	39 (29.8)	37 (28.2)	55 (23.1)	77 (32.5)	58 (24.4)	67 (28.3)
University	28 (21.4)	42 (32.1)	41 (31.3)	41 (31.3)	43 (18.1)	61 (25.7)	65 (27.3)	65 (27.4)
Tobacco smoking, n (%)								
Never	81 (61.8)	80 (61.1)	66 (50.4)	62 (47.3)	157 (66.0)	144 (60.8)	139 (58.4)	119 (50.2)*
Former	37 (28.2)	44 (33.6)	54 (41.2)	58 (44.3)	65 (27.3)	76 (32.1)	76 (31.9)	97 (40.9)
Current	13 (9.92)	7 (5.34)	11 (8.40)	11 (8.40)	16 (6.72)	17 (7.17)	23 (9.66)	21 (8.86)
Alcohol consumption, n (%)								
Never	30 (22.9)	25 (19.1)	17 (13.0)	12 (9.16)*	57 (23.9)	44 (18.6)	39 (16.4)	35 (14.8)*
Former	14 (10.7)	24 (18.3)	19 (14.5)	11 (8.40)	32 (13.4)	48 (20.3)	39 (16.4)	26 (11.0)
Current	87 (66.4)	82 (62.6)	95 (72.5)	108 (82.4)	149 (62.6)	145 (61.2)	160 (67.2)	176 (74.3)
Physical activity, MET-hours/week	21.4 (12.3)	22.7 (13.8)	26.9 (13.8)	24.4 (13.4)*	19.5 (11.8)	21.6 (13.1)	24.2 (12.8)	23.7 (13.9)*
Sedentary behavior, TV hours/day	2.47 (1.24)	2.40 (1.41)	2.35 (1.19)	2.23 (1.01)	2.68 (1.39)	2.55 (1.41)	2.43 (1.24)	2.45 (1.18)
Energy intake, kcal/day	1953 (387)	2028 (414)	2048 (393)	2232 (450)*	1953 (371)	2020 (412)	2042 (402)	2239 (477)*
Body mass index, kg/m^2	27.8 (3.91)	28.2 (4.17)	27.7 (3.86)	27.8 (3.50)	28.6 (4.42)	28.5 (4.22)	27.9 (4.15)	28.6 (4.09)
Number of chronic diseases[c]	0.82 (0.86)	0.85 (0.84)	0.70 (0.78)	0.79 (0.75)	1.06 (0.88)	0.98 (0.83)	0.95 (0.91)	0.94 (0.84)
Mediterranean Diet Score[d]	3.46 (1.46)	3.72 (1.59)	4.02 (1.58)	4.23 (1.48)*	3.50 (1.52)	3.77 (1.58)	4.0 (1.60)	4.20 (1.47)*

Values are numbers (%) or means (standard deviations).
*P-value <0.05 for differences in means (ANOVA) or proportions (Pearson's chi-squared) across quartiles of fish consumption.
[a] Total fish consumption (subjects without pain): Quartile 1, ≤44.6 g/day; Quartile 2, ≥45 to ≤63.7 g/day; Quartile 3, ≥64.0 to ≤92.9 g/day; Quartile 4, >92.9 g/day.
[b] Total fish consumption (subjects with and without pain): Quartile 1, ≤43.9 g/day; Quartile 2, ≥44.1 to ≤64.8 g/day; Quartile 3, >64.8 to ≤91.3 g/day; Quartile 4, >91.7 g/day.
[c] Diabetes, cardiovascular disease, chronic lung disease, musculoskeletal disease, cancer, and depression.
[d] Without including fish consumption.

Differences across quartiles of marine omega-3 fatty acid intake resembled those of fish consumption (Supplementary Table 2).

The mean (standard deviation) points in the pain scale among the subjects with pain in 2012 were 4.87 (1.00). Out of these 426 subjects, 25.5% had sporadic pain and 74.5% had persistent pain. Regarding pain severity, 37.2% had light pain, whereas 62.8% had moderate-to-severe pain. With respect to the number of pain locations, 50.6% had pain in 1–2 pain sites and 49.4% in ≥3 pain sites. Specifically, 34.9% of the subjects with pain in 2012 had pain in the head/neck, 50.1% in the back, 61.6% in bones/joints, 42.9% in the arms, 64.2% in the legs, and 24.6% in other sites.

3.2. Main results

After a mean follow-up time of 4.9 years, we ascertained 125 cases of incident pain (23.9%) and 184 of pain worsening (19.3%). Total fish consumption was not associated with pain incidence or pain changes. When examining the main types of fish separately, white fish consumption was not associated with pain, while oily fish was associated with lower pain incidence and less pain worsening: the model 2 OR (95% CI) were 0.68 (0.50,0.94) and 0.70 (0.55,0.88) for every 25 g/day increment in oily fish consumption – roughly 1.5 servings/week (Table 2). Clear inverse dose–response relationships with pain incidence and worsening were observed when plotting oily fish consumption as a restricted cubic spline (Fig. 1).

Higher marine omega-3 fatty acid intake was associated with less pain worsening [the model 2 OR (95% CI) per 0.5 g/day increment was 0.83 (0.72,0.96)] (Table 3). The main omega-3 fatty acids showed consistent associations, as the corresponding OR were 0.53 (0.33,0.87) for EPA and 0.73 (0.57,0.94) for DHA. Here again, marine omega-3 fatty acid intake was inversely linked to pain worsening in a dose–response manner (restricted cubic spline shown in Fig. 2).

In ancillary analyses, higher oily fish consumption and marine omega-3 fatty acid intake were associated with reduced or maintained pain severity and number of pain locations (Supplementary Tables 3 and 4).

3.3. Interactions and sensitivity analyses

We found no evidence that frailty, sex, or any sociodemographic, lifestyle, morbidity, or dietary variable included in the models significantly modified the associations of fish consumption and marine omega-3 fatty acid intake with pain incidence or pain worsening (Supplementary Figs. 2 and 3). Nevertheless, the associations were stronger in the subjects with higher omega-6 intake -note that the omega-6: omega-3 ratio showed some tendency to pain worsening (Supplementary Table 5).

The study associations were consistent when categorizing incident pain into intermediate and highest pain (Supplementary Tables 6 and 7), when switching from our pain scale to the Numeric Rating Scale for pain intensity, when excluding subjects with cancer, and after adjusting the analyses for individual chronic diseases and NSAID use (Supplementary Tables 8 and 9). A nonsignificant trend between marine omega-3 fatty acid intake ≥0.25 g/day and lower risk of pain was also observed (Supplementary Table 9).

4. Discussion

In this cohort of Spanish older adults, increased oily fish consumption was associated with lower pain incidence and reduced pain worsening over 5 years, and higher marine omega-3 fatty acid intake (and that of EPA and DHA) was linked to less pain worsening. Results were consistent in several sensitivity analyses.

Table 2
Associations of fish consumption with pain incidence and pain worsening over 4.9 years in older adults.

	Total fish consumption				
	Quartile 1[a]	**Quartile 2**[a]	**Quartile 3**[a]	**Quartile 4**[a]	**Per 25 g/day increment**
Pain incidence					
Cases/n	35/131	35/131	27/131	28/131	125/524
Model 1: OR (95% CI)[d]	Ref.	1.02 (0.58,1.77)	0.82 (0.46,1.49)	0.86 (0.48,1.54)	0.97 (0.85,1.11)
Model 2: OR (95% CI)[e]	Ref.	0.89 (0.49,1.61)	0.87 (0.47,1.63)	0.77 (0.40,1.45)	0.96 (0.83,1.11)
Pain worsening					
Cases/n	57/238	47/237	41/238	39/237	184/950
Model 1: OR (95% CI)[d]	Ref.	0.80 (0.52,1.25)	0.73 (0.46,1.16)	0.70 (0.44,1.12)	0.94 (0.84,1.05)
Model 2: OR (95% CI)[e]	Ref.	0.79 (0.50,1.24)	0.74 (0.46,1.18)	0.65 (0.40,1.06)	0.92 (0.82,1.04)
	White fish consumption				
	Quartile 1[b]	**Quartile 2**[b]	**Quartile 3**[b]	**Quartile 4**[b]	**Per 25 g/day increment**
Pain incidence					
Cases/n	30/131	33/131	29/131	33/131	125/524
Model 1: OR (95% CI)[d]	Ref.	1.14 (0.64,2.04)	1.00 (0.56,1.81)	1.30 (0.73,2.32)	1.12 (0.92,1.36)
Model 2: OR (95% CI)[e]	Ref.	1.23 (0.67,2.26)	0.96 (0.52,1.78)	1.28 (0.68,2.38)	1.09 (0.88,1.34)
Pain worsening					
Cases/n	45/239	49/237	47/237	43/237	184/950
Model 1: OR (95% CI)[d]	Ref.	1.13 (0.71,1.77)	1.11 (0.70,1.75)	1.05 (0.66,1.68)	1.07 (0.92,1.24)
Model 2: OR (95% CI)[e]	Ref.	1.16 (0.73,1.85)	1.13 (0.71,1.80)	1.04 (0.64,1.68)	1.06 (0.90,1.23)
	Oily fish consumption				
	Quartile 1[c]	**Quartile 2**[c]	**Quartile 3**[c]	**Quartile 4**[c]	**Per 25 g/day increment**
Pain incidence					
Cases/n	40/131	30/131	32/131	23/131	125/524
Model 1: OR (95% CI)[d]	Ref.	0.74 (0.42,1.31)	0.82 (0.47,1.43)	0.54 (0.30,0.98)*	0.69 (0.51,0.92)*
Model 2: OR (95% CI)[e]	Ref.	0.75 (0.41,1.36)	0.98 (0.54,1.78)	0.55 (0.30,1.04)	0.68 (0.50,0.94)*
Pain worsening					
Cases/n	57/238	53/237	42/238	32/237	184/950
Model 1: OR (95% CI)[d]	Ref.	0.95 (0.62,1.47)	0.72 (0.46,1.13)	0.55 (0.34,0.89)*	0.71 (0.56,0.90)**
Model 2: OR (95% CI)[e]	Ref.	0.93 (0.60,1.44)	0.74 (0.47,1.17)	0.53 (0.33,0.87)*	0.70 (0.55,0.88)**

*p < 0.05. **p < 0.01. OR: odds ratio. CI: confidence interval.
[a] Total fish consumption (pain incidence analyses): Quartile 1, ≤44.6 g/day; Quartile 2, ≥45 to ≤63.7 g/day; Quartile 3, ≥64.0 to ≤92.9 g/day; Quartile 4, >92.9 g/day. Total fish consumption (pain worsening analyses): Quartile 1, ≤43.9 g/day; Quartile 2, ≥44.1 to ≤64.8 g/day; Quartile 3, >64.8 to ≤91.3 g/day; Quartile 4, >91.7 g/day.
[b] White fish consumption (pain incidence analyses): Quartile 1, ≤19.6 g/day; Quartile 2, ≥19.8 to ≤32.1 g/day; Quartile 3, ≥32.2 to ≤51.3 g/day; Quartile 4, ≥51.5 g/day. White fish consumption (pain worsening analyses): Quartile 1, ≤18.5 g/day; Quartile 2, ≥18.6 to ≤31.5 g/day; Quartile 3, >31.5 to ≤51.2 g/day; Quartile 4, >51.2 g/day.
[c] Oily fish consumption (pain incidence analyses): Quartile 1, ≤10.9 g/day; Quartile 2, ≥11.2 to ≤21.4 g/day; Quartile 3, ≥21.6 to ≤35.0 g/day; Quartile 4, ≥35.2 g/day. Oily fish consumption (pain worsening analyses): Quartile 1, ≤10.7 g/day; Quartile 2, >10.7 to ≤21.0 g/day; Quartile 3, >21.0 to ≤34.6 g/day; Quartile 4, >34.6 g/day.
[d] Model 1: Logistic regression model adjusted for sex, age, and educational level (primary or less, secondary, or university).
[e] Model 2: As Model 1 and additionally adjusted for smoking status (never, former, or current), alcohol consumption (never, former, or current), leisure-time physical activity (MET-hours/week), sedentary behavior (TV hours/day), body mass index (kg/m^2), energy intake (kcal/day), number of chronic diseases (diabetes, cardiovascular disease, chronic lung disease, musculoskeletal disease, cancer, and depression), and Mediterranean Diet Score (without including fish consumption).

4.1. Interpretation

4.1.1. Relevant findings from other published studies

On one hand, most evidence on the relation between omega-3 fatty acid intake and pain comes from randomized controlled trials. Those evaluating the effects of fish oil in the reduction of musculoskeletal pain generally favored the treated groups [15]. Studies on exercise-induced pain have also found a reduction of musculoskeletal pain and inflammatory biomarkers (i.e., C-reactive protein) after fish oil supplementation [16,37]. A meta-analysis of randomized trials with marine oil supplements in arthritis patients showed a reduction in pain intensity and C-reactive protein after supplementation with marine oils. While there was a significant effect on pain in patients with rheumatoid arthritis and other/mixed diagnoses, no effect was evident in patients with osteoarthritis, but the confidence in the latter estimate was very low [17]. Since the publication of this meta-analysis, further studies have shown that omega-3 supplementation could help reduce the use of non-steroidal anti-inflammatory, analgesic, and disease-modifying antirheumatic drugs [13].

On the other hand, most observational research has focused on arthritis and not on pain itself. Case-control studies have shown that broiled or baked fish is associated with lower risk of rheumatoid arthritis, whereas the omega-3 proportion in red blood cells is inversely associated with some diagnostic biomarkers of rheumatoid arthritis (i.e., rheumatoid factor and anti-cyclic citrullinated peptide positivity) among at-risk patients [19]. Also, most EPA and some DHA-derived oxylipin species (i.e., bioactive lipids that serve as suppressors of systemic inflammation) were lower in newly diagnosed rheumatoid arthritis cases compared to controls, and these significantly increased after said cases started glucocorticoid treatment. This suggests that both oxylipin species may be depleted by inflammatory states, but their levels might recover when other molecules take the lead in countering chronic inflammation [23]. In cohort studies, increased fish consumption – especially oily fish – and omega-3 fatty acid intake have been associated with lower risk of rheumatoid arthritis [19]. In addition, omega-3 fatty acid intake has been inversely associated with high pain intensity and refractory pain, but not with inflammatory pain or C-reactive protein among rheumatoid arthritis patients under anti-inflammatory treatment [20]. Finally, the omega-6:omega-3 ratio may be upregulated in rheumatoid arthritis and has been associated with increased knee pain symptoms in patients with osteoarthritis [22,23].

4.1.2. Possible mechanisms and explanations

In our study, the associations of oily fish consumption with risk of pain were similar to those of marine omega-3 intake, although the former were somewhat stronger (especially those with pain incidence). Any explanation for these differences must be conjectural, but they may reflect the presence of several nutrients in fish beyond omega-3 fatty acids. Specifically, oily fish is a source of vitamins (B1, B12, D), minerals (zinc, selenium), and amino acids (methionine), which may play a modulatory role in chronic pain through management of inflammation and oxidative stress [14]. Indeed, there is some evidence from intervention studies in dysmenorrhea showing that administration of omega-3 fatty acid supplements together with vitamin B1 pills may reduce pain more than omega-3 fatty acid supplements alone [16].

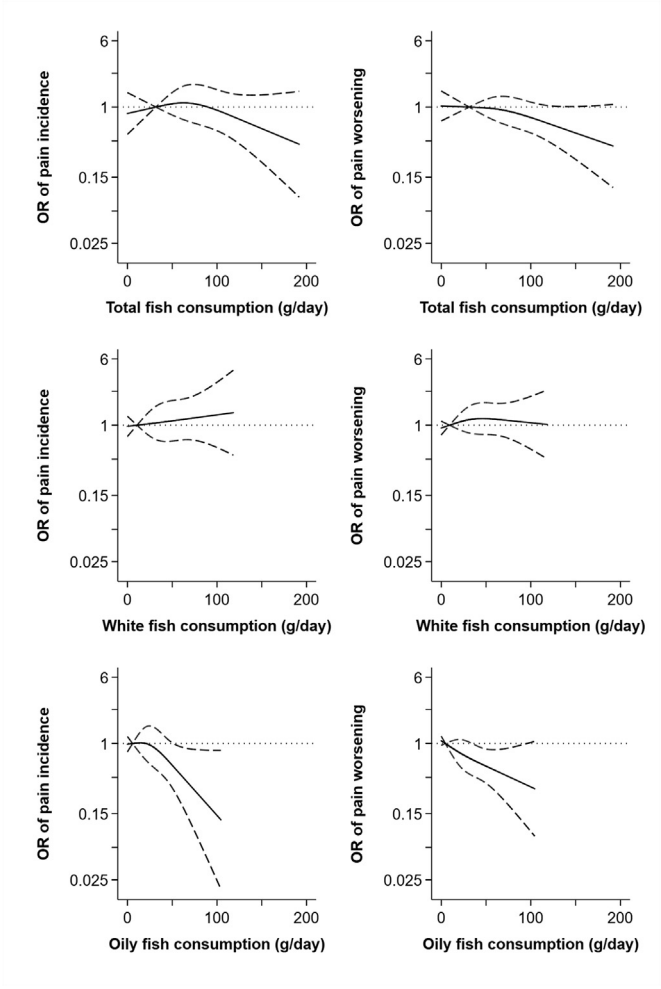

Fig. 1. Associations of fish consumption with pain incidence and pain worsening over 4.9 years in older adults.
Plotted values are odds ratios (95% confidence intervals) from a logistic regression model as Model 2 in Table 2 [adjusted for sex, age, educational level (primary or less, secondary, or university), smoking status (never, former, or current), alcohol consumption (never, former, or current), leisure-time physical activity (MET-hours/week), sedentary behavior (TV hours/day), body mass index (kg/m^2), energy intake (kcal/day), number of chronic diseases (diabetes, cardiovascular disease, chronic lung disease, musculoskeletal disease, cancer, and depression), and Mediterranean Diet Score (without including fish consumption)]. Restricted cubic spline knots (pain incidence analyses): total fish consumption (31.8, 63.1, and 118 g/day; reference: 31.8 g/day), white fish consumption (10.7, 31.5, and 70.6 g/day; reference: 10.7 g/day), oily fish consumption (5.78, 21.4, and 50.7 g/day; reference: 5.78 g/day). Restricted cubic spline knots (pain worsening analyses): total fish consumption (31.2, 64.6, and 117 g/day; reference: 31.2 g/day), white fish consumption (9.30, 31.2, and 68.9 g/day; reference: 9.30 g/day), oily fish consumption (4.62, 20.8, and 50.2 g/day; reference: 4.62 g/day). P for nonlinear trend for pain incidence/pain worsening were 0.29/0.49 for total fish, 0.99/0.50 for white fish, and 0.31/0.81 for oily fish consumption.

The distinct associations of white and oily fish with pain found in our study are probably due to the larger amounts of omega-3 fatty acids found in the latter, which have well known pro-resolving, analgesic, and anti-nociceptive actions. On one hand, these fatty acids reduce adhesion molecule expression on immune cells and endothelium, stimulate the uptake of apoptotic neutrophils, and promote the clearance of necrotic cellular debris – note that an increase in the levels of E-series resolvins in synovial fluids has been associated with pain reduction in patients with arthritis [38,39]. On the other hand, omega-3 fatty acids modulate circulating lymphocytes and activate the hypothalamic G protein-coupled receptor 40/Free fatty acid receptor 1 expression at the spinal level, which in turn plays an important role in chronic pain control [14].

Several mechanisms might explain the anti-inflammatory actions of the omega-3 fatty acids coming from fish and seafood. Direct actions include the counteraction of proinflammatory mediators by EPA and DHA-derived lipoxins, protectins, and maresins [38,39], and the reduction in gene expression of cytokines, cyclooxygenase 2, and degrading proteinases [15,25]. The indirect anti-inflammatory actions may be related to the omega-6: omega-3 ratio. They include the substitution of omega-3 for omega-6 fatty acids at the cell membrane level (note that prostaglandins derived from arachidonic acid are thought to lead to inflammation through the production of cytokines such as interleukin-1β, interleukin-2, interleukin-6, interleukin-18, and tumor necrosis factor-α) [12]; the interference in the signaling pathways of inflammation (e.g., the conversion of EPA into prostaglandin E3 is carried by the same enzyme used to convert arachidonic acid into the pro-inflammatory prostaglandin E2 [14]); and the competition of omega-3 fatty acid products with proinflammatory molecules for several cell receptors [12,14].

4.2. Generalizability

To what extent do our estimates apply to other populations and settings? It is noteworthy that Spain is one of the countries with the highest per capita fish consumption in Europe and the world -roughly 14.8 kg in 2015, compared to 3.35 kg in France and 1.15 kg in Sweden [40]. Conversely, the prevalence of chronic pain in Spain seems to be lower than that of said countries (12%, 15%, and 18%, respectively [2]). While these data may have public health implications, they may also suggest that the relationship between fish consumption and pain prevalence at the country level is rather weak and subject to ceiling effect. Nevertheless, we observed a strong dose–response relationship for the association between oily fish and risk of pain, and there was no evidence of floor effect (Fig. 1), so we hypothesize that our results may also be relevant for those countries with lower fish consumption.

On the contrary, it is possible that marine omega-3 intake may not confer pain benefits to omega-3 supplement users, as a possible saturation of the association between EPA/DHA and pain intensity reduction has been observed in arthritis patients at supplement doses ≥2.6 g/day – note that only 1.58% of our study subjects had a dietary intake above this threshold [17]. Fish consumption among omega-3 supplement users could have some favorable effects on pain, though, as it is a source of other nutrients that may modulate inflammation and oxidative stress [14].

Another distinctive aspect of our study population is its moderate-to-high vegetable, legume, fruit/nut, and cereal consumption, in agreement with the moderately high Mediterranean Diet Scores observed (Table 1). Since we found no evidence that this

Table 3
Associations of marine omega-3 fatty acid intake with pain incidence and pain worsening over 4.9 years in older adults.

	Total omega-3 fatty acid intake[a]				
	Quartile 1[b]	**Quartile 2[b]**	**Quartile 3[b]**	**Quartile 4[b]**	**Per 0.5 g/day increment**
Pain incidence					
Cases/n	38/131	33/131	29/131	25/131	125/524
Model 1: OR (95% CI)[e]	Ref.	0.89 (0.51,1.55)	0.78 (0.44,1.37)	0.68 (0.37,1.22)	0.85 (0.71,1.01)
Model 2: OR (95% CI)[f]	Ref.	0.82 (0.46,1.48)	0.79 (0.43,1.46)	0.71 (0.38,1.34)	0.86 (0.72,1.03)
Pain worsening					
Cases/n	60/238	46/237	43/238	35/237	184/950
Model 1: OR (95% CI)[e]	Ref.	0.74 (0.48,1.15)	0.68 (0.43,1.06)	0.58 (0.36,0.93)*	0.84 (0.73,0.97)*
Model 2: OR (95% CI)[f]	Ref.	0.74 (0.47,1.15)	0.67 (0.43,1.06)	0.58 (0.36,0.94)*	0.83 (0.72,0.96)*
	Eicosapentaenoic acid (EPA) intake[b]				
	Quartile 1[c]	**Quartile 2[c]**	**Quartile 3[c]**	**Quartile 4[c]**	**Per 0.5 g/day increment**
Pain incidence					
Cases/n	35/131	36/131	29/131	25/131	125/524
Model 1: OR (95% CI)[e]	Ref.	1.14 (0.65,1.99)	0.88 (0.49,1.57)	0.78 (0.43,1.41)	0.58 (0.32,1.04)
Model 2: OR (95% CI)[f]	Ref.	1.03 (0.57,1.86)	0.92 (0.50,1.71)	0.81 (0.43,1.52)	0.60 (0.32,1.12)
Pain worsening					
Cases/n	55/238	56/237	38/238	35/237	184/950
Model 1: OR (95% CI)[e]	Ref.	1.07 (0.70,1.65)	0.66 (0.42,1.05)	0.66 (0.41,1.06)	0.54 (0.33,0.89)*
Model 2: OR (95% CI)[f]	Ref.	1.06 (0.69,1.64)	0.67 (0.42,1.07)	0.65 (0.40,1.07)	0.53 (0.33,0.87)*
	Docosahexaenoic acid (DHA) intake[c]				
	Quartile 1[d]	**Quartile 2[d]**	**Quartile 3[d]**	**Quartile 4[d]**	**Per 0.5 g/day increment**
Pain incidence					
Cases/n	37/131	32/131	31/131	25/131	125/524
Model 1: OR (95% CI)[e]	Ref.	0.88 (0.50,1.55)	0.89 (0.51,1.57)	0.70 (0.39,1.26)	0.75 (0.55,1.01)
Model 2: OR (95% CI)[f]	Ref.	0.77 (0.43,1.40)	0.85 (0.47,1.56)	0.73 (0.39,1.38)	0.77 (0.56,1.06)
Pain worsening					
Cases/n	59/238	45/237	46/238	34/237	184/950
Model 1: OR (95% CI)[e]	Ref.	0.74 (0.48,1.15)	0.76 (0.49,1.18)	0.58 (0.36,0.93)*	0.74 (0.58,0.95)*
Model 2: OR (95% CI)[f]	Ref.	0.71 (0.45,1.11)	0.74 (0.47,1.16)	0.57 (0.35,0.93)*	0.73 (0.57,0.94)*

*p < 0.05. **p < 0.01. OR: odds ratio. CI: confidence interval. SD: standard deviation.
[a] Total marine omega-3 fatty acid intake: α-linolenic acid, EPA, docosapentaenoic acid, DHA, and stearidonic acid.
[b] Total marine omega-3 intake (pain incidence analyses): Quartile 1, ≤0.40 g/day; Quartile 2, >0.40 to ≤0.73 g/day; Quartile 3, >0.73 to ≤1.25 g/day; Quartile 4, >1.25 g/day. Total omega-3 intake (pain worsening analyses): Quartile 1, ≤0.42 g/day; Quartile 2, >0.42 to ≤0.74 g/day; Quartile 3, ≥0.75 to ≤1.23 g/day; Quartile 4, >1.23 g/day.
[c] EPA intake (pain incidence analyses): Quartile 1, ≤0.12 g/day; Quartile 2, >0.12 to ≤0.22 g/day; Quartile 3, >0.22 to ≤0.35 g/day; Quartile 4, >0.35 g/day. EPA intake (pain worsening analyses): Quartile 1, ≤0.12 g/day; Quartile 2, >0.12 to ≤0.22 g/day; Quartile 3, >0.22 to ≤0.35 g/day; Quartile 4, >0.35 g/day.
[d] DHA intake (pain incidence analyses): Quartile 1, ≤0.21 g/day; Quartile 2, >0.21 to ≤0.39 g/day; Quartile 3, >0.39 to ≤0.68 g/day; Quartile 4, >0.68 g/day. DHA intake (pain worsening analyses): Quartile 1, ≤0.22 g/day; Quartile 2, >0.22 to ≤0.41 g/day; Quartile 3, >0.41 to ≤0.67 g/day; Quartile 4, >0.67 g/day.
[e] Model 1: Logistic regression model adjusted for sex, age, and educational level (primary or less, secondary, or university).
[f] Model 2: As Model 1 and additionally adjusted for smoking status (never, former, or current), alcohol consumption (never, former, or current), leisure-time physical activity (MET-hours/week), sedentary behavior (TV hours/day), body mass index (kg/m^2), energy intake (kcal/day), number of chronic diseases (diabetes, cardiovascular disease, chronic lung disease, musculoskeletal disease, cancer, and depression), and Mediterranean Diet Score (without including fish consumption).

dietary pattern modified the study associations (Supplementary Figs. 2 and 3), it is likely that our results may also apply to countries with lower overall diet quality.

Finally, our study comprised adults over 60 years old and pain affected 44.9% of participants in 2012, a rather higher prevalence than among younger adults [3]. We nevertheless found no evidence that either frailty or age modified the study associations (Supplementary Figs. 2 and 3). Lastly, the Seniors-ENRICA-1 population was largely white (99.2%), thus warranting caution when applying our results to multi-ethnic/multiracial populations.

4.3. Limitations

Some limitations should be acknowledged. First, the correlations between the fish consumption, EPA intake, and DHA intake estimated via our dietary history and seven 24-h recalls over one year were moderate ($r = 0.42$, 0.55, and 0.60, respectively), though similar to the methods used to measure habitual diet in other studies [29,41]. Nevertheless, there was little gross misclassification between the dietary history and said 24-h recalls, as the percentage of subjects simultaneously classified in the highest quintile by the latter method and the lowest quintile by the former was 10.5%, 10.0%, and 5.3% for fish consumption, EPA intake, and DHA intake, respectively [29]. In this regard, it is encouraging to see how modeling fish consumption and marine omega-3 fatty acid intake as continuous (per 25 and 0.5 g/day increments, respectively) and categorical (quartiles) variables rendered consistent results (Tables 2 and 3). Second, we were not able to examine whether the relationship between fish consumption, marine omega-3 fatty acid intake, and risk of pain was correlated with that of the serum omega-3 levels in 2012 -as we lacked the corresponding data. Though the latter would have been less prone to measurement and reporting errors, it may not have captured the nuances of habitual fish consumption, which is a source of several nutrients beyond omega-3 fatty acids [14].

Third, our pain scale has not been validated, although the questions used to build it were taken from the Survey on Chronic Pain in Europe, and the study associations were relatively consistent when using the Numeric Rating Scale for pain intensity instead (Supplementary Tables 8 and 9) [2]. Also, most covariates were self-reported, so we cannot rule out some residual confounding, even after adjusting the regression models for many sociodemographic variables, lifestyle, morbidity, and diet quality. For instance, omega-3 supplement use may have been underreported, and we lacked the dosing data that would have been needed to combine omega-3 pills' intake with foods'. Then again, it is reassuring to see similar

results from: (1) minimally-adjusted vs fully-adjusted models, and (2) those adjusting for individual chronic diseases and NSAID use (Supplementary Tables 8 and 9).

Fourth, our 5-year follow-up may have helped to overcome some of the limitations of current randomized controlled trials on omega-3 and pain, but it came with somewhat high loss to follow-up rates. As in other aging cohorts, participants were probably lost to follow-up due to ill health, disability, institutionalization, or death [42], leading to a selection of younger, more educated, and healthier subjects, which may have biased the study results in any direction (Supplementary Table 1). Because of the high prevalence of pain in 2012 (44.9%), the analytical sample for pain incidence was rather small, as well as the number of incident pain cases. The consequently reduced precision is exemplified by the association of total marine omega-3 fatty acid intake (per 0.5 g/day increment) with incident pain [0.86 (0.72,1.03)], which was not statistically significant despite being of a similar magnitude to the association of marine omega-3 with pain worsening observed in the main sample [0.83 (0.72,0.96)].

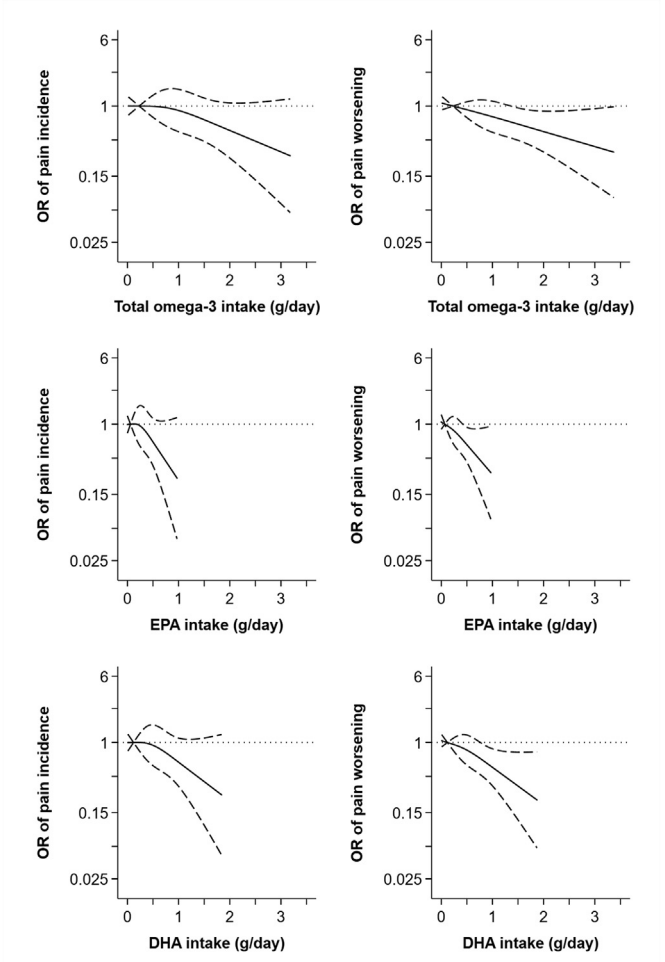

Fig. 2. Associations of marine omega-3 fatty acid intake with pain incidence and pain worsening over 4.9 years in older adults.
Total marine omega-3 intake: α-linolenic acid, EPA, docosapentaenoic acid, DHA, and stearidonic acid; EPA: Eicosapentaenoic acid; DHA: Docosahexaenoic acid. Plotted values are odds ratios (95% confidence intervals) from a logistic regression model as Model 2 in Table 3 [adjusted for sex, age, educational level (primary or less, secondary, or university), smoking status (never, former, or current), alcohol consumption (never, former, or current), leisure-time physical activity (MET-hours/week), sedentary behavior (TV hours/day), body mass index (kg/m^2), energy intake (kcal/day), number of chronic diseases (diabetes, cardiovascular disease, chronic lung disease, musculoskeletal disease, cancer, and depression), and Mediterranean Diet Score (without including fish consumption)]. Restricted cubic spline knots (pain incidence analyses): Total marine omega-3 intake (0.23, 0.72, and 1.65 g/day; reference: 0.23 g/day), EPA intake (0.06, 0.21, and 0.49 g/day; reference: 0.06 g/day), DHA intake (0.12, 0.38, and 0.94 g/day; reference: 0.12 g/day). Restricted cubic spline knots (pain worsening analyses): Total marine omega-3 intake (0.23, 0.74, and 1.68 g/day; reference: 0.23 g/day), EPA intake (0.07, 0.21, and 0.49 g/day; reference: 0.07 g/day), DHA intake (0.12, 0.40, and 0.96 g/day; reference: 0.12 g/day). P for nonlinear trend for pain incidence/pain worsening were 0.53/0.95 for total marine omega-3 fatty acid, 0.46/0.74 for EPA, and 0.51/0.62 for DHA intake.

4.4. Conclusions

In this cohort of Spanish older adults, higher oily fish consumption was associated with lower pain incidence and reduced pain worsening over 5 years, while higher marine omega-3 fatty acid intake (and that of EPA and DHA) was linked to less pain worsening. Results were consistent in main analyses (assessing pain with a scale developed from the Survey on Chronic Pain in Europe) and sensitivity analyses (using a Numeric Rating Scale for pain intensity).

These findings suggest that oily fish and marine-omega-3 could be considered for adjunctive pain management, while promotion of oily fish consumption may also play a role in primary pain prevention -either in the clinic or via cost-effective public health campaigns.

Larger studies should, however, address whether these findings are generalizable to younger and ethnically diverse populations. More research focused on the correlation of the study associations with those of serum omega-3 levels is warranted. Future studies in older adults should also assess the effectiveness of pain prevention and management interventions targeting fish consumption.

Authors' Contributions

FRA, ACC, and RO conceived the study. ACC, RO, and EGE performed the statistical analyses. ACC, RO, and FRA drafted the manuscript. All authors contributed to results interpretation. All authors reviewed the manuscript for important intellectual content, red, and approved the final manuscript.

All authors have agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

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Data statement

The datasets used and/or analyzed during the current study are available from the corresponding authors on reasonable request.

Conflict of Interest

None of the authors have any competing interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2022.09.007.

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