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ORIGINAL CONTRIBUTION

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Long chain omega-3 fatty acids intake, fish consumption and mental disorders in the SUN cohort study

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Abstract *Background* Very long chain omega-3 fatty acids (w-3 PUFA) intake and fish consumption have been suggested as protective factors against neuropsychiatric disorders but there is scarcity of large cohort studies assessing this association. *Aim of the study* To assess the association between w-3-PUFA intake and fish consumption and mental disorders. *Methods* A prospective cohort study was performed in 7,903 participants. W-3 PUFA intake and fish consumption were ascertained through a validated semi-quantitative food frequency questionnaire. The outcomes after 2 years of follow-up were: (1) Incident mental disorder (depression, anxiety, or stress), (2) incident depression, and (3) incident anxiety. Logistic regression models and generalized additive models were fit to assess the relationship between w-3 PUFA intake or fish consumption and the incidence of these outcomes. Odds ratios (OR) and their 95% confidence intervals (CI) were calculated. *Results* 173 cases of depression, 335 cases of anxiety, and 4 cases of stress were observed during 2-year follow-up. ORs (95% CI) of mental disorder for successive quintiles of energy-adjusted w-3 PUFA intake were 1 (reference), 0.72 (0.52–0.99), 0.79 (0.58–1.08), 0.65 (0.47–0.90), and 1.04 (0.78–1.40). Subjects with a moderate consumption of fish (third and fourth quintiles of consumption: median of each quintile 83.3 and 112 g/day, respectively) had a relative risk reduction higher than 30%. *Conclusions* A potential benefit of w-3 PUFA intake on total mental disorders is suggested, although no linear trend was apparent.

Key words omega-3 fatty acids – fish – depression – anxiety – mental disorder

Introduction

The beneficial effects of polyunsaturated omega-3 fatty acids (w-3 PUFA) intake on human health, especially on cardiovascular disease, are largely known [6]. Thus, food guidelines recommend regular fish consumption in general population as the main source of w-3 PUFAs. In addition, the use of w-3 PUFA supplements has been also recommended for patients with coronary heart disease or hypertriglyceridemia [27]. Recent researches have evaluated the role of w-3 PUFA on the adequate nervous system function [15] and on neuropsychiatric alterations treatment [30]. Small clinical trials have

studied the beneficial effect of w-3 PUFA supplementation in patients with schizophrenia [9], on bipolar disorders [16] or on childhood [41] and adult depression [42, 45] or postpartum depression [18]. Only a few epidemiological studies have assessed these associations, reporting an inverse relationship between w-3 PUFAs intake and hostility [26], anxiety disorders [19], and depression. The nutritional epidemiology of depression probably deserves a higher attention because it is one of the most relevant single contributors to the global burden of disease, being the world leading cause of years of life lived with disability for both men and women [31]. Moreover, the huge menacing adverse impact of depression on global health is projected to increase in the next 15 years [40].

Six out of eight case–control studies have shown that levels of w-3 PUFAs in plasma or red blood cell membranes were lower in psychiatric patients than in controls [7, 8, 11, 17, 33, 46, 50, 52]. But, with the notable exception of the nested case–control study of Rotterdam [52] most of these studies included very few subjects and did not control for confounding. Two cross-sectional studies based on the adult population from Finland observed a higher risk of depressive symptoms among infrequent consumers of fish but this association was only present for women [51, 53]. Two available longitudinal studies conducted to exclusively assess post-partum depression found that w-3 PUFAs plasma concentrations were lower in depressed women than in healthy ones [5, 43]. The single large cohort study that has assessed the association between fish consumption and the risk of depression was based on 29,133 Finnish male participants 50–69 years old at baseline. There was no significant association of fish consumption or intake of w-3 PUFA intake with any of the study endpoints after the follow-up [21].

Due to the limitations of available case–control studies (including the inherent weaknesses of this design) and the disparate results for men and women reported in the few available prospective cohorts, there is need for further large longitudinal studies including both men and women to assess the potential preventive role of fish consumption and w-3 against depression. Our aim was to ascertain the association of fish consumption or w-3 PUFA intake with the incidence of mental disorders in a dynamic prospective study of university graduates in Spain, including both men and women.

Materials and methods

The SUN cohort was designed in collaboration with the Harvard School of Public Health using similar methodology than that of large American cohorts such as the Nurses' Health Study or the Health Professionals Follow-up Study [36]. Information is collected using self-administered questionnaires sent by postal mail every 2 years. The recruitment of participants started in December 1999 and it is permanently on-going. All participants are university graduates. Up to January 2006, 10,096 participants had responded both the baseline and the first 2-years follow-up questionnaire (baseline = Q_0 and follow-up = Q_2, hereafter). The follow-up rate for the first 2 years period was 88%. Those participants who reported extremely low or high values for total energy intake (less than 600 kcal/day in men and 400 kcal/day in women or more than 4,200 kcal/day in men and 3,500 kcal/day in women) (n = 767), those who were users of either antidepressant or tranquilizer medication at baseline and subjects with a self-reported physician-diagnosed depression, anxiety or stress at baseline (n = 1,426) were excluded. Finally, data from 7,903 participants remained available for the analysis.

The study was approved by the Human Research Ethical Committee at the University of Navarra. Voluntary completion of the first questionnaire was considered to imply informed consent.

Exposure assessment

The dietary exposure was ascertained through a semi-quantitative food frequency questionnaire (136 food items) previously validated in Spain [35]. Nutrient scores were calculated as frequency × nutrient composition of specified portion size for each food item. Nutrient intake scores were computed using an ad hoc computer program specifically developed for this aim. A trained dietitian updated the nutrient data bank using the latest available information included in food composition tables for Spain [37, 39]. Questionnaire items in relation to fish and seafood consumption and their long chain omega-3 fatty acids (w-3 PUFA) content (g/100 g of food item) were: (a) lean fish: young hake, hake, sea bream, grouper and sole (0.62); (b) fatty fish: salmon, mackerel, tuna, Atlantic bonito and sardine (1.87); (c) cod (0.70); (d) smoked and salt fish: salmon and herring (4.44); (e) mussel, oyster and clam (2.20); (f) shrimp, prawn and crayfish (0.90), and (g) octopus, baby squid and squid (0.71). Long chain w-3 PUFA intake and fish consumption were adjusted for total energy intake using the residuals method proposed by Willett. Energy intake was introduced as the independent variable and fish or w-3 PUFA intake as the outcome in a linear regression model. The energy-adjusted value is the result of the sum of the residual of the model and the fish or W-3 PUFA mean intake [54]. Finally, the

continuous variables were categorized in quintiles. Additionally, Q_2 included an item regarding change in fish consumption since Q_0 (no change, increment, or decrement in consumption in a qualitative way). To assess the joint effect of baseline fish consumption and the changes in consumption along the 2 years of follow up, a new variable was built considering baseline consumption in tertiles and change in fish consumption (dichotomized as no change or decrement versus increment in consumption) obtained a new variable with six categories ranging from the less favorable situation (low baseline consumption of fish and no change or a decrease in consumption during the follow up) to the most favorable one (high baseline consumption of fish and a increase in consumption during the follow-up).

Covariate assessment

The baseline semi-quantitative food frequency questionnaire also collected data regarding alcohol, folate, and vitamins B_6 and B_{12} intake and regarding stimulant beverages consumption (chocolate, coffee, and caffeine-containing soda drinks). The baseline assessment (Q_0) also included other questions (totalling 46 items for men and 54 items for women). Socio-demographic (e.g., gender, age, marital status, and employment status), anthropometric (e.g., weight and height), lifestyle and health-related habits (e.g., smoking status and physical activity during leisure time), and medical history variables (e.g., prevalence of chronic diseases and medication use) were collected. The physical activity questionnaire included information about 17 activities. To quantify the volume of activity during leisure time, an activity metabolic equivalent (MET) index was computed by assigning a multiple of resting metabolic rate (MET score) to each activity [3], and the time spent in each of the activities was multiplied by the MET score specific to each activity, and then summed over all activities obtaining a value of overall weekly MET-hours. Additionally, Q_2 included an item regarding change in physical activity since Q_0 (no change, increment, or decrement in physical activity).

Participants were classified as having cardiovascular disease if they reported at least one of the following conditions: myocardial infarction, stroke, atrial fibrillation, paroxysmal tachycardia, coronary artery bypass grafting or other revascularization procedures, heart failure, aortic aneurism, pulmonary embolism, or peripheral venous thrombosis. We considered a participant to present an incapacitating disease if he or she reported a medical diagnosis of asthma, emphysema, or rheumatoid arthritis.

Outcome assessment

Any participant, initially free of depression and of antidepressant treatment, who positively responded to the following question in Q_2: Have you ever been diagnosed of depression by a health professional? was classified as an incident case of depression. The same criteria were applied for anxiety and stress. Any participant, initially free of depression and of antidepressant treatment, who reported the use of antidepressants in Q_2 was classified as an incident case of depression. Any participant, initially free of a diagnosis of anxiety, who reported the use of tranquilizers in Q_2 was classified as an incident case of anxiety. The outcomes after 2 years of follow-up considered were:

(a) Incident mental disorder defined as a self-reported physician diagnosis of depression, anxiety or stress or/and use of antidepressant medication or tranquilizers reported in Q_2.
(b) Incident depression defined as a self-reported physician diagnosis of depression or/and use of antidepressant medication reported in Q_2.
(c) Incident anxiety defined as a self-reported physician diagnosis of anxiety or/and use of tranquilizers reported in Q_2.

Statistical analysis

Non-conditional logistic regression models were fit to assess the relationship between w-3 PUFA intake or fish consumption and the incidence of mental disorder (depression, anxiety and stress together and specifically incidence of depression and incidence of anxiety) in our cohort. Odds ratios (OR) and their 95% confidence intervals (CI) were calculated considering the lowest quintile for w-3 PUFA intake or for fish consumption as the reference categories. Tests of linear trend across increasing quintiles of intake were conducted by assigning the medians of intake to each quintile and treating the intake as a continuous variable. Potential confounders included in the multivariate model were: age (continuous), body mass index (<25 kg/m^2, 25–29.9 kg/m^2, and ≥ 30 kg/m^2), physical activity during leisure-time (no exercise, 0.1–8.0 METs-h/week, 8.01–17.0 METs-h/week, 17.01–28.0 METs-h/week, >28.0 METs-h/week), change in physical activity since baseline (no change, decrease, increase), marital status (single, married, widowed, separated, or other), smoking (never, past, and current smokers), unemployment (no/yes), presence of any severe disease at baseline (cancer, cardiovascular or incapacitating disease), energy intake (continuous), energy-adjusted folate, vitamin B_{12} and vitamin

Table 1 Characteristics[a] [mean (SD)] of the participants according to quintiles of energy-adjusted[b] w-3 fatty acids intake

	Energy-adjusted[b] w-3 fatty acid intake				
	Q1 (n = 1,580)	Q2 (n = 1,580)	Q3 (n = 1,581)	Q4 (n = 1,581)	Q5 (n = 1,580)
Age (years)	39.6 (11.0)	40.3 (11.2)	40.8 (11.2)	41.7 (12.1)	44.0 (13.1)
Body mass index (kg/m^2)	23.0 (3.3)	23.1 (3.4)	23.3 (3.5)	23.5 (3.3)	23.7 (3.6)
Smoking status (%)					
Ex-smoker	23.4	25.5	28.9	28.5	30.0
Current smoker	25.6	23.2	24.5	26.0	24.0
Severe diseases (%)					
Cancer	3.1	2.5	2.7	2.7	3.2
Cardiovascular	2.7	3.3	3.0	3.4	4.6
Incapacitating diseases[c]	7.7	7.7	7.1	8.4	8.0
Marital status (%)					
Single	54.0	49.3	47.9	44.4	42.2
Married	43.8	47.5	49.5	53.5	54.5
Unemployed (%)	5.0	6.3	5.2	4.6	3.9
Energy-adjusted[b] fish consumption (g/day)	35.6 (16.7)	63.9 (14.2)	84.4 (15.7)	111.8 (22.4)	176.9 (75.8)
Energy-adjusted[b] folate intake (μg/day)	354.8 (162.3)	375.4 (132.3)	392.6 (133.5)	420.0 (146.0)	468.9 (168.8)
Energy-adjusted[b] vitamin B_6 intake (mg/day)	2.2 (0.6)	2.4 (0.6)	2.6 (0.5)	2.8 (0.6)	3.4 (0.7)
Energy-adjusted[b] vitamin B_{12} intake (mg/day)	6.4 (3.5)	8.0 (3.1)	8.9 (3.2)	10.1 (3.5)	14.7 (5.8)
Stimulant beverages consumption (mg/day)[d]	78.1 (67.6)	72.7 (59.1)	67.2 (52.9)	67.4 (55.3)	66.9 (63.0)
Alcohol intake (g/day)	5.9 (9.7)	6.0 (8.9)	6.3 (8.9)	6.9 (10.1)	7.5 (11.3)
Energy intake (kcal/day)	2550.9 (693.8)	2401.1 (610.7)	2270.2 (578.2)	2260.9 (629.4)	2485.9 (621.5)
Physical activity during leisure-time (METs-h/w)	27.2 (26.2)	25.6 (22.1)	26.9 (24.4)	28.3 (25.5)	31.3 (26.7)
Increase in physical activity (%)	29.7	27.0	29.9	32.1	32.0

[a]Mean and standard deviation (SD) unless otherwise stated
[b]Nutrient intakes were adjusted for total energy intake using the residuals method proposed by Willett [54]
[c]Asthma, emphysema, rheumatoid arthritis
[d]Coffee, chocolate, and coke

B_6 intakes (continuous), alcohol intake (continuous) and stimulant beverages consumption (continuous).

To ascertain the effect of the joint exposure to baseline fish consumption and to changes in consumption during follow-up, the participants with the lowest baseline fish consumption (first tertile of consumption) and without change or with a decreased fish consumption during the 2 years of follow-up were considered as the reference category and they were compared with the other five categories created by combining both exposures.

To avoid the limitations of the traditional analysis of continuous exposures [14] non-parametric models [20] were also used. Briefly, approaches based on linear models require previous assumptions to be made regarding the functional form of the dose–risk curve, and approaches based on categorical analysis require cut-offs to be selected, which is often done arbitrarily and opportunistically, and which can alter the results of the study. Application of non-parametric methods, on the other hand, allows for dose–response relationships to be approximated and OR and their CI calculated without the need for any arbitrary assumptions whatsoever as regards cut-offs or functional form. We applied generalize additive models with smoothing splines with four degree of freedom for continuous independent variables.

All P values presented are 2-tailed; $P < 0.05$ was considered statistically significant.

The cumulative incidence of depression varied from 5.9% among subjects belonging to the lowest quintile of w-3 PUFA intake (Q1) to 4.1% among those belonging to the fourth quintile of intake (Q4). Taking in consideration these extreme values (Q1 and Q4) and an alpha error of 0.05, we calculated that the statistical power to detect a relative risk ≤0.69 was 62.8%.

Results

Table 1 shows the main characteristics of the participants according to quintiles of energy-adjusted omega-3 fatty acids (w-3 PUFA) intake. W-3 PUFA intake was higher among older participants, ex-smokers, and married subjects. Participants belonging to the highest quintiles of w-3 PUFA intake were physically more active. Moreover, participants with a higher w-3 PUFA intake also showed a higher alcohol, folate, vitamin B_6, and vitamin B_{12} intake but lower consumption of stimulant beverages.

We identified 173 cases of depression, 335 cases of anxiety, and 4 cases of stress during a median follow-up of 27.5 months.

Table 2 Association between baseline w-3 fatty acids intake or fish consumption and the risk of mental disorder.[a] Odds Ratios (95% CI)

	Q1	Q2	Q3	Q4	Q5	p for trend
	Energy-adjusted[b] w-3 fatty acids intake					
Median intake g/d	0.39	0.66	0.87	1.17	1.89	
Number of cases	93	71	77	65	100	
Model 1 (95% CI)	[1]	0.74 (0.54–1.01)	0.80 (0.59–1.09)	0.66 (0.48–0.92)	1.04 (0.78–1.40)	0.404
Model 2 (95% CI)	[1]	0.72 (0.52–0.99)	0.79 (0.58–1.08)	0.65 (0.47–0.90)	1.04 (0.78–1.40)	0.376
	Energy-adjusted[b] fish consumption					
Median intake g/d	36.43	61.53	83.33	112.03	161.90	
Number of cases	92	77	66	68	103	
Model 1 (95% CI)	[1]	0.81 (0.59–1.10)	0.67 (0.49–0.93)	0.69 (0.50–0.95)	1.06 (0.79–1.42)	0.532
Model 2 (95% CI)	[1]	0.80 (0.58–1.09)	0.67 (0.48–0.93)	0.68 (0.49–0.94)	1.06 (0.79–1.43)	0.499
Model 3 (95% CI)	[1]	0.87 (0.55–1.38)	0.71 (0.41–1.22)	0.75 (0.40–1.41)	1.08 (0.51–2.31)	0.660

Model 1: Adjusted for age (years) and gender. Model 2: Additionally adjusted for incapacitating disease in Q_0, energy intake (kcal/day), physical activity during leisure time (quintiles METs-h/w), and change in physical activity since baseline (No change, increase, decrease). Model 3: Similar to Model 2 but additionally adjusted for energy-adjusted[b] w-3 fatty acids intake (g/day)

[a]Defined as self-reported physician diagnosis of depression, anxiety or stress or use of antidepressant medication or tranquilizers reported in Q_2

[b]W-3 PUFA intake and fish consumption were adjusted for total energy intake using the residuals method proposed by Willett [54]

Table 2 shows the association between quintiles of w-3 PUFA intake or quintiles of fish consumption and the risk of a mental disorder in the cohort. Subjects in the lowest intake were considered as the reference category. The multivariate adjusted ORs (95% CI) of a mental disorder for successive quintiles of energy-adjusted w-3 PUFA intake were 1 (reference), 0.72 (0.52–0.99), 0.79 (0.58–1.08), 0.65 (0.47–0.90) and 1.04 (0.78–1.40) suggesting an inverse association between w-3 PUFA intake and the risk of a mental disorder for the second and the fourth quintile of intake. However, the linear trend for quintiles of w-3 PUFA intake was not statistically significant (P for trend = 0.38). Similar results were found when fish consumption was analyzed. Subjects with a moderate consumption of fish (third and fourth quintiles of consumption: median of each quintile 83.3 and 112 g/day, respectively) had a relative risk reduction of suffering a mental disorder of more than 30% although a dose–response relationship was not found (P for trend = 0.50). The potential beneficial effect of fish consumption for the 3rd–4th quintile was lost when w-3 PUFA intake was included in the multivariate analyses.

Additionally, we ascertained the role of energy-adjusted oily fish consumption on mental disorder risk obtaining the following multivariate ORs and 95% CI (Q1–Q5): [1], 0.77 (0.56–1.06), 0.71 (0.51–0.98), 0.69 (0.49–0.98) and 1.02 (0.75–1.37).

Table 3 shows the association between the incidence of mental disorders and the joint exposure to both baseline fish consumption and changes in consumption during follow-up. Participants in the first tertile of consumption who maintained or reduced their fish consumption during follow-up were considered as the reference category. Unexpectedly, there was a statistically significant higher risk of mental disorder for participants with both high baseline consumption (upper tertile) and increased consumption during follow-up (OR = 1.57; 95% CI = 1.11–2.22).

To assess a differential effect of w-3 PUFA on mental health according to the gender, we calculated the ORs (95% CI) for the association between the quintiles of w-3 fatty acid intake and mental disorder risk in men and women separately. Whereas there were not statistically significant associations for men [[1]; 0.65 (0.35–1.19); 0.95 (0.54–1.66); 0.76 (0.43–1.35); 0.95 (0.56–1.61)], the results for women were similar to those found in the overall sample [[1]; 0.75 (0.52–1.09); 0.73 (0.50–1.07); 0.60 (0.40–0.90); 1.08 (0.76–1.55)].

We applied generalized additive models with smoothing splines to assess the relationship between w-3 PUFA intake and incident depression (Fig. 1). Inverse associations were observed for intermediate values of w-3 PUFA intake (1–2 g/day) when we consider as the reference category the percentile 0.1 (median of the first quintile of energy-adjusted w-3 PUFA intake).

Figure 2 shows the lnORs (and 95% CI) for the association between w-3 PUFA intake and the incidence of anxiety among the SUN participants using smoothing splines. The results were very similar to those found for depression.

Discussion

A suggestion for a potential beneficial effect of w-3 PUFA intake on total mental disorders was found among the participants of the SUN cohort. However, no linear trend was apparent.

Several biological mechanisms have been suggested to postulate inverse associations between fish (or long chain w-3 PUFA) consumption and the risk of mental disorders. W-3 PUFA are essential

Table 3 Joint association between the incidence of mental disorder and both baseline fish consumption (tertiles) and change in fish consumption (no change/decrease versus increase in Q_2) after 2-year follow-up. Odds Ratios (95% CI)

Change in fish consumption from baseline	Baseline energy-adjusted[a] fish consumption					
	T1		T2		T3	
	No change/decrease	Increase	No change/decrease	Increase	No change/decrease	Increase
Number of participants	2,112	464	2,111	488	1,960	638
Number of cases	110	30	90	21	94	53
Model 1 (95% CI)	[1]	1.29 (0.85–1.95)	0.79 (0.59–1.05)	0.78 (0.49–1.26)	0.88 (0.66–1.16)	1.56 (1.10–2.19)
Model 2 (95% CI)	[1]	1.28 (0.84–1.96)	0.80 (0.60–1.06)	0.80 (0.49–1.29)	0.88 (0.66–1.18)	1.57 (1.11–2.22)

Model 1: Adjusted for age (years) and gender. Model 2: Additionally adjusted for incapacitating disease in Q_0, energy intake (kcal/day), physical activity during leisure time (quintiles METs-h/w), and change in physical activity since baseline (No change, increase, decrease)
[a]Fish consumption was adjusted for total energy intake using the residuals method proposed by Willett [54]

components of the Central Nervous System neuronal membranes and are implicated in their dynamic structure, changing their fluidity. Higher w-3 PUFA concentrations lead to increased membrane fluidity, which consecutively increases serotonin transport [12]. Thus, these fatty acids have an effect on receptor function, neurotransmitter reuptake and on signal transmission. A mental disorder like depression has been associated with over-activity of the inflammatory response of the immune system increasing pro-inflammatory cytokines production [38]. W-3 fatty acids have been suggested as inhibitors of some of these cytokines, especially of tumor necrosis factor-alpha (TNF-α) and interleukin-1beta (IL-1β). IL-1β or TNF-α may lower neurotransmitter precursors availability like tryptophan, alter the metabolism of neurotransmitters and neurotransmitter transporter mRNA, and modulate the hypothalamic-pituitary-adrenocortical axis activity causing resistance to glucocorticoid hormones [30].

Four of six small clinical trials designed to assess the effectiveness on depression of w-3 PUFA supplementation have obtained remarkable favorable results [18, 41, 42, 45], even though the results may change depending on the administered doses and of the kind of fatty acid utilized in the trial (EPA, DHA or both). Nevertheless, although several reports have suggested that low intakes w-3 PUFA and fish (main source of w-3 PUFA) may be associated with a higher risk of cognitive impairment, anxiety, bipolar disorders or depression, and trials conducted with small samples in a clinical setting have reported optimistic results, recent studies with observational design have found contradictory results.

In two ecological studies, Hibbeln found a negative correlation between fish consumption and world-wide depression prevalence [22] and, similarly, an inverse association between docosahexanoic acid concentration in human milk and post-partum depression prevalence [23]. A review published in 2006 has showed the most recent findings regarding the association between blood levels of w-3 fatty acids and depression [7]. According to the review, six case–control studies have analyzed the role of w-3 fatty acids on depression. Four of them observed lower levels of DHA [17, 23, 33, 52] in cases of depression, three lower levels of EPA [8, 23, 33] and one more lower levels total w-3 fatty acids [8]. Moreover, an association between higher severity of depression scores and lower w-3 fatty acids levels have been found in several studies [33, 34, 44]. Whereas two cohort studies have been carried out to ascertain the role of these nutrients on post-partum depression [21, 43] only one cohort study has analyzed the effect of fish consumption on depression [36]. After 9 years of follow-up, the authors reported a slightly increase in the risk of self-reported depressive mood for those individuals belonging to the third tertile of fish consumption as compared with subjects belonging to lower tertiles, although the associations did not reach statistical significance. Similar results were found in our cohort. Subjects with the highest consumption of fish (fifth quintile of consumption) had an increased risk for a mental disorder than those participants belonging to the lowest quintile of consumption although the results were not statistically significant and the magnitude of the association was small.

The use of self-reported depressive mood as outcome measurement could have biased (supposedly toward the null) the reported associations. Feeling depressed differs from having a diagnosis of depression and exchanging both measurements could undervalue the true effect of fish consumption on depression. Considering only as cases those subjects with a hospital discharge due to depression could also underestimate the association between w-3 PUFA intake and depression.

It should be taken into account that subjects included in clinical trials are all psychiatric patients with an established diagnosis of depression and with a short period of follow-up in a very controlled environment, very different from subjects belonging to a

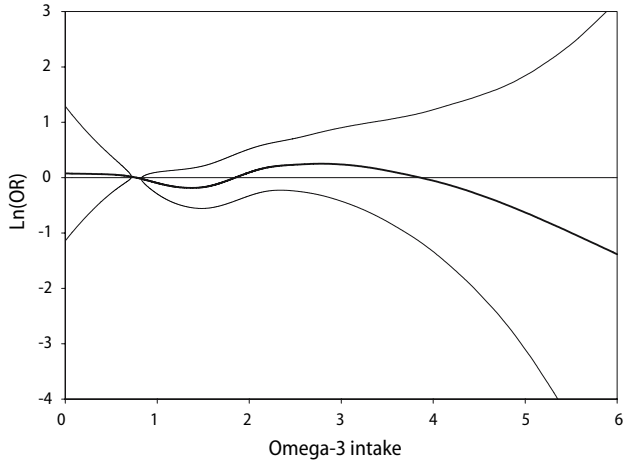

Fig. 1 Ln(OR) (adjusted for age (years), gender, incapacitating disease in Q_0, energy intake (kcal/day), physical activity during leisure time (quintiles METs-h/w), and change in physical activity since baseline (no change, increase, decrease). Reference category: percentile 0.1) and 95% CI for the association between baseline energy-adjusted (W-3 PUFA intake was adjusted for total energy intake using the residuals method proposed by Willett [54]) w-3 fatty acids intake (g/day) and risk of depression (Depression was defined as physician diagnosis of depression or use of antidepressant medication reported in Q_2) in Q_2

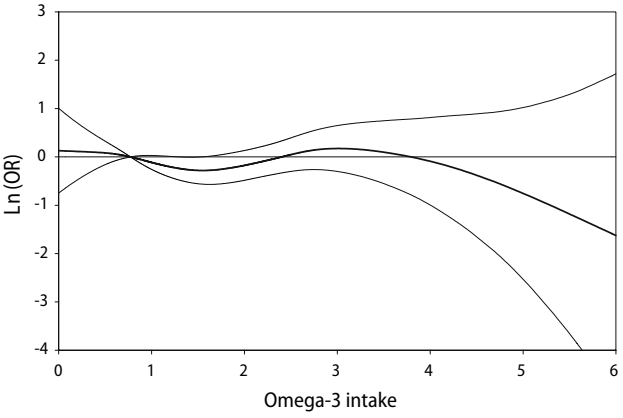

Fig. 2 Ln(OR) (adjusted for age (years), gender, incapacitating disease in Q_0, energy intake (kcal/day), physical activity during leisure time (quintiles METs-h/w), and change in physical activity since baseline (no change, increase, decrease). Reference category: percentile 0.1) and 95% CI for the association between baseline energy-adjusted (W-3 PUFA intake was adjusted for total energy intake using the residuals method proposed by Willett [54]) w-3 fatty acids intake (g/day) and risk of anxiety (anxiety was defined as physician diagnosis of anxiety or use of tranquilizer medication reported in Q_2) in Q_2

general population. On the other hand, ecological and case–control studies have several limitations that could bias the reported results. In this point, the contributions of cohort studies to analyze these associations, such as the SUN Cohort Study, become essential.

Unexpectedly, when baseline and follow-up fish consumption were jointly considered in our analysis, a high baseline consumption together with an increment in consumption were associated with an increased risk of mental disorders. One possible explanation to the reported results could be the mercury content of fish. An accumulation of mercury compounds could increase the risk of depression among participants with high baseline fish consumption and who increased their consumption during the follow-up. Some studies have reported a strong correlation between toenail mercury content or serum mercury concentration and fish consumption [1, 47]. Different Spanish studies have analyzed the Hg content in autochthonous fish species. The EPIC Cohort in Gipuzkoa (in the Cantabrian coast) calculated the mercury content in several types of fish. Those with the most mercury concentration were hake (117.6 μg/kg), pout (169.5 μg/kg), canned tuna in oil (223.3 μg/kg), tuna (308 μg/kg), Atlantic bonito (308 μg/kg) and canned Atlantic bonito in oil (223.3 μg/kg) [49]. An analysis of fish from Catalonia (Mediterranean coast) reported the following Hg content: tuna (0.38–0.58 μg/g fish), swordfish (1.59–2.22 μg/g fish), hake (0.12–0.29 μg/g fish) and red mullet (0.14–0.36 μg/g fish). The authors estimated an Hg intake of 9.89 μg/day for men and 8.90 μg/day for women [10].

Organic mercury compounds could cause neurological damage. There is some available evidence about the negative effect of mercury compounds on Alzheimer disease, memory loss, autism or depression [24, 55]. The US Environmental Protection Agency suggests that the Oral Reference Dose for methilmercury should be from 0.3 to 0.1 μg/kg/day in pregnant women to avoid intrauterine neurological effects on the fetus and retarded psychomotor development. If we apply these values to a general population, considering the lower limit of 0.1 and assuming that methylmercury makes up 90% of total mercury, 25% of the men and 15% of the women of the Gipuzkoa EPIC-cohort would exceed the mercury recommended values. Thus, because our cohort is composed by highly educated people where fish consumption is greater than in general population, it is probable that a higher proportion of our cohort exceeds the suitable values supporting the hypothesis of the toxic effect of mercury content of fish.

The possibility of reverse causality could be an alternative explanation for our reported results. Subjects with a mental disorder at the beginning of the study but without a physician diagnosis of depression or anxiety might have increased their fish consumption because it is likely that their mood disorder may lead them to alter their behavior and change their food habits.

In addition, some participants of this young cohort could have initiated a diet to reduce weight during the follow-up. Dieters are prone to have depressive symptoms independently of their weight status [4]. In fact, weight control has been associated to poor body image, low self-esteem, and depression in several studies [28, 29]. Additionally, food choices are conditioned to psychological and behavioral factors such as mental well being. Dieters who choose diet according to ideological reasons more than according pleasure seeking are more likely to have symptoms of depression and of eating disorders.

Ideological reasons could include a philosophy of life in which the consumption of fruits, vegetables, or fish instead meat of un-healthy food items acquires an essential role [29].

A potential limitation in our study is the definition of cases and the methods for case ascertainment of mental disorder, depression, or anxiety. We used self-reports of a physician-diagnosed disorder. The most common instruments used in epidemiological research to assess these outcomes are self-administered scales such as the Center for Epidemiological Studies Depression Scale, the Beck Depression Inventory or the WHO Well Being Index. However, these scales assess depressive or anxiety symptoms but the election of the cutt-off point is arbitrary and it depends on the sample characteristics (like age or cultural level) and on the pathology type.

The use of a self-reported diagnosis done by a physician does not necessarily mean that the measurement error is increased, because highly educated participants are very likely to report correct diagnoses and there is a low likelihood of finding false positives. However, there are evidences about the possibility of under-estimation of true cases when a physician diagnosis is used as the criteria. A recent study found that physicians' recognition of 'major depressive disorder' was poor (sensitivity, 40%; specificity, 87%) as compared with the Structured Clinical Interview for DSM-IV (SCID) used as gold standard [32]. Nevertheless, the possibility of underestimation of a mental disorder might lead also to under-estimate the magnitude of the true protective effect of w-3 PUFA and fish on mental disorder. Thus, the beneficial effect fount for w-3 PUFA in the intermediate quintiles would be higher than that reported in this analysis. In this reasoning we are assuming that a non-differential misclassification may exist and it is likely that it would bias the estimates toward the null. Nevertheless, sometimes when the exposure has more than two categories the bias from non-differential misclassification of exposure for a given comparison may be away from the null value. However, this fact is unusual.

Other caveat is the specificity of the different diagnoses within mental disorders. It is possible that a depressive disorder maybe misclassified by the diagnosing physician. A participant reporting depression could have in reality an anxiety or stress disorder instead depression. Indeed, the results obtained in our study for depression are very similar to those found for anxiety or for mental disorder. For that reason, we prefer considering the total mental disorders as the outcome instead of separating depression or anxiety in different categories.

Finally, although the validity and reliability of our semi-quantitative food frequency questionnaire has been evaluated [35], there are not Spanish studies specifically designed to validate fish consumption or w-3 PUFA intake data. We have to assume that the w-3 PUFA intake validation data obtained in other similar cohort studies such as the Health Professionals Follow-up Study are adequate and can be applied to our cohort [25]. In fact, the questionnaire used in our study to assess w-3 PUFA intake is a Spanish validated adaptation of that used in the cited cohort studies [13, 48]. In the Health Professionals Follow-up Study, Spearman correlation coefficient between estimates derived from the food frequency questionnaire and those obtained through subcutaneous adipose tissue aspiration was $r = 0.47$ ($P = 0.0001$) for eicosapentaenoic acid [25]. Moreover, Baylin et al compared the estimated dietary intake of w-3 fatty acids with the fatty acid content in adipose tissue samples by capillary gas chromatography. Fish intake correlated significantly with adipose tissue w-3 fatty acids. These authors concluded that adipose tissue is a suitable biomarker of dietary fatty acid intake, particularly for w-3 and w-6 *cis* PUFA and trans fatty acids [2].

In conclusion, our results point to a beneficial effect of w-3 PUFA intake, especially moderate intake, on mental disorders. Considering the body of knowledge existing about this issue, we believe that further longitudinal studies with a longer follow-up period, with a better evaluation of mental status and using also biomarkers of w-3 fatty acid intake are needed to better ascertain the dose–response relationship.

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