



## Original article

## Fish and sea products consumption and allergic rhinitis: A multicenter case–control study



Carlos Regueira <sup>a</sup>, Narmeen Mallah <sup>a, b, c, d, \*</sup>, Jurgita Saulyte <sup>a</sup>,  
Francisco-Javier González-Barcala <sup>e, f, g, h</sup>, Bahi Takkouche <sup>a, d</sup>

<sup>a</sup> Department of Preventive Medicine, University of Santiago de Compostela, Santiago de Compostela, Spain

<sup>b</sup> WHO Collaborating Centre for Vaccine Safety, Santiago de Compostela, Spain

<sup>c</sup> Genetics, Vaccines and Pediatric Infectious Diseases Research Group (GENVIP), Instituto de Investigación Sanitaria de Santiago de Compostela, Galicia, Spain

<sup>d</sup> Centro de Investigación Biomédica en Red de Epidemiología y Salud Pública (CIBER-ESP), Madrid, Spain

<sup>e</sup> Translational Research in Airway Diseases (TRIAD), Fundación Instituto de Investigación Sanitaria de Santiago de Compostela (FIDIS), Santiago de Compostela, Spain

<sup>f</sup> Department of Medicine, University of Santiago de Compostela, Spain

<sup>g</sup> Centro de Investigación Biomédica en Red de Enfermedades Respiratorias (CIBERES), Madrid, Spain

<sup>h</sup> Respiratory Department, Complejo Hospitalario Universitario de Santiago de Compostela, Santiago de Compostela, Spain

## ARTICLE INFO

## Article history:

Received 7 October 2024

Accepted 3 April 2025

## Keywords:

Rhinitis

Allergic

Case–control studies

Fatty acids

Fishes

Seafood

## SUMMARY

**Background:** The association of allergic diseases with the intake of fish-derived proteins and fatty acids remains unclear, with studies showing divergent results. We aimed to examine the association of those nutrients with the occurrence of allergic rhinitis (AR).

**Methods:** A multicenter case–control study was conducted with 411 AR cases and 477 controls. Adjusted odds ratios (OR) of AR and their 95 % confidence intervals (CI) were estimated using multivariate logistic regression models. Stratified analyses by fish type and macronutrient were undertaken.

**Results:** Blue fish consumption, except tuna, is associated with an important decrease in the odds of AR (1 serving/week: OR = 0.46; 95%CI: 0.27–0.80; 2 servings/week: OR = 0.30; 95%CI: 0.17–0.54; 3–4 servings/week: OR = 0.38; 95%CI: 0.20–0.68). Conversely, compared to no intake, white fish consumption is associated with higher odds of AR (3 servings/week: OR = 5.49; 95%CI: 3.27–9.24).

A high n-6/n-3 polyunsaturated fatty acids (PUFAs) ratio is associated with higher odds of AR (OR = 1.79; 95%CI: 1.03–3.13 for the highest intake level compared to the lowest). High intake of n-3 PUFAs is associated with substantially lower odds of AR ranging between 46 % and 58 % (stearidonic acid OR = 0.42; 95%CI: 0.24–0.74; eicosapentaenoic acid OR = 0.45; 95%CI: 0.25–0.80; and docosapentaenoic acid OR = 0.54; 95%CI: 0.31–0.96).

**Conclusions:** A high intake of blue fish, except tuna, is associated with lower odds of AR while that of white fish has an opposite association with the disease occurrence.

© 2025 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY-NC license (<http://creativecommons.org/licenses/by-nc/4.0/>).

\* Corresponding author. Department of Preventive Medicine, Faculty of Medicine, University of Santiago de Compostela, 15782 Santiago de Compostela, Spain.  
E-mail address: [narmeen.mallah@usc.es](mailto:narmeen.mallah@usc.es) (N. Mallah).

**Take home message**

Fish and seafood, and their fat and protein contents are associated with allergic rhinitis (AR). High blue and white fish intake contribute differently to AR, with the first, except tuna, acting as a protector and the second as a risk factor of AR.

**1. Introduction**

Allergic rhinitis (AR) is a highly prevalent form of rhinitis, with an average worldwide prevalence of 18 % and large variations between geographic regions [1]. Its prevalence in Europe ranges from 1 % to 44 % [1], but is often underestimated. AR often coexists with other respiratory diseases such as asthma, with almost 40 % of individuals with rhinitis also having asthma and 80 % of asthmatic individuals having rhinitis [2–4]. Furthermore, AR represents a substantial economic burden, nearly \$4 billion per year in the US [5].

Behavioral determinants, including dietary habits, were associated with AR occurrence, yet evidence is still unclear [6,7]. A study in Greece showed that good adherence to the Mediterranean diet was associated with lower odds of AR [8], while an increase in the ratio n6/n3 of the large chain Polyunsaturated Fatty Acids (LC-PUFA) and a decrease in n-3 PUFA augmented the risk of AR [9]. Another Spanish study also pointed to a higher prevalence of rhinitis symptoms among children and adolescents with a higher adherence to the Mediterranean diet [7].

Many studies have shown the beneficial effect of the consumption of fish and its derivatives and nutrients on AR [10–14]. However, other studies also reported contradictory findings [15–18]. The discrepancy between the results of different studies may be due to differences in study design and populations' characteristics, but also to differences in the composition of different fish species.

Fish species are classified into “white” and “blue” according to their amount of fat. Species with more than 5 % fat content are considered blue fish. Most of them are high in n-3 LC-PUFA [19]. Blue fish intake is suggested to be associated with a lower risk of inflammation of the nasal mucosa that occurs in AR episodes, an anti-inflammatory effect aided by n-3 LC-PUFA [9]. The fat content in whitefish species does not exceed 2 % of its total weight. So far, we are not aware of any study the aim of which was to disentangle the relation of each species of fish with AR.

Accordingly, we conducted a multi-center case–control study to investigate the association of different fish species with AR development. We present an analysis stratified by fish type and macronutrients.

**2. Methods****2.1. Study design and settings**

We carried out a multicenter case–control study involving adults ( $\geq 18$  years) in Galicia, Northwest Spain, a region with a coastline of 1660 km, home to 2.7 million inhabitants whose staple is fish. The study participants were recruited among visitors to six large pharmacies in two main cities (Santiago de Compostela and Pontevedra) and among patients attending the pulmonology and allergology units of the two main hospitals in those cities. The study protocol was approved by the Bioethics Committee of the University of Santiago de Compostela. Participants signed an informed

consent before enrollment in the study. Patient anonymity and data confidentiality were preserved using methods approved by the Ethics Committee.

**2.2. Sample size calculation**

For an alpha level of 0.05, a power of 0.80, assuming an exposure prevalence of 10 % among controls and an OR to be detected of 1.8, we needed 409 cases and 409 controls. Our sample size was approximately equal to these estimations.

**2.3. Cases and controls definitions**

Pharmacy customers who were buying over-the-counter medicines for rhinitis symptoms such as antihistaminic drugs (a complete list of medicines is available upon request to the authors) were invited to participate in the study as potential cases. In the hospital units, cases were selected from patients attending for allergy symptoms, such as rhinorrhea, excessive sneezing, and nasal obstruction.

The control group consisted of pharmacy customers or patients attending the hospitals for any other reason than allergy or respiratory symptoms. We included customers who sought medicine related to minor traumatic injuries, digestive disorders, high blood pressure, diabetes, and antidepressants, and customers who were buying medications for their relatives. Hospital controls were recruited among patients visiting the hospital for injuries, cardiovascular, gastrointestinal and gynaecologic motives.

**2.4. Outcome validation**

Allergic rhinitis, non-allergic rhinitis and other respiratory diseases such as common cold or sinusitis share typical symptoms including nasal obstruction and blocked sinuses, which may lead to an erroneous diagnosis of AR [20].

To assess the accuracy of case ascertainment, we carried out a validation study of AR diagnosis along with the main study. We used as a gold standard a sample of 255 persons randomly selected from the hospital of Santiago de Compostela for whom the diagnosis of either AR (70 subjects), non-allergic rhinitis (25 subjects), or no rhinitis (160 subjects) was firmly established using clinical and biologic criteria (skin prick tests, IgE levels). We asked those 255 subjects to complete the disease ascertainment questionnaire and calculated the sensitivity and specificity of our diagnosis. The final figures were as follows: sensitivity = 0.74 and specificity = 0.92.

**2.5. Outcome assessment**

Using the Allergic Rhinitis and its Impact on Asthma (ARIA) questionnaire, together with the criteria of the Joint Task Force on Practice Parameters [21,22], we asked the participants to record the presence of six main symptoms of AR on the peak day of the current episode and to rate their frequency from zero (no attack per day) to four (more than 20 attacks per day). These symptoms were: nasal congestion, sneezing, runny nose, postnasal drip, itchy nose, and itchy or watery eyes. We also asked the participants to rate the thickness of their nasal secretion from zero (very watery) to four (very thick), as well as its color from zero (colorless) to four (green). We also asked about potential triggers of these symptoms such as exposure to pollen, house dust mites or animal dander.

Four criteria were required to ascertain AR: (i) minimum symptom score of 4 out of 12 for three main symptoms of AR (nasal congestion, sneezing, and runny nose), (ii) thickness of nasal secretion from very watery to medium, (iii) white or colorless nasal secretion, and (iv) at least one of the irritants causing rhinitis

symptoms should have been pollen, house dust mites or animal dander. We selected the cutoff point of 4 for the first criterion as this figure maximized the sensitivity and specificity of AR diagnosis in the concurrent validation sub-study explained previously. Subjects were considered as having non-allergic rhinitis [23], and were excluded from the analysis if they reported: (i) a minimum score of rhinitis symptoms of 4 out of 12 (nasal congestion, sneezing, and runny nose), (ii) postnasal drip at least 6 times a day, or a thickness score of nasal secretion from medium to very thick, and (iii) rhinitis symptoms were triggered by either tobacco smoke, changes in temperature, high humidity or exposure to deodorant sprays. We did not differentiate between seasonal (intermittent) and perennial (persistent) types of AR.

Controls were subjects with (i) a score of rhinitis symptoms (nasal congestion, sneezing, and runny nose)  $\leq 3$  out of 12, (ii) no subjective feeling nor confirmed diagnosis of rhinitis, and (iii) no use of medications that could hide possible rhinitis symptoms (medicines for asthma, mucolytic, decongestant or expectorant drugs (complete list available upon request)). As occasional sneezing and rhinorrhea in the morning after exposure to cold and polluted air are considered to be a normal nasal response [24], we assumed that some occasional nasal symptoms may be present in the healthy population and thus accepted subjects with minor symptoms as controls.

## 2.6. Exposure assessment

To assess the regular diet and obtain daily intakes of macronutrients and micronutrients, together with energy intake, we used an 86-item Food Frequency Questionnaire (FFQ), developed and validated in Spain [25]. Participants were asked about their average frequency of consumption of standard portions of selected dietary items, representative of the Spanish diet. Each food frequency was reported with an eight-grade scale ranging from “never” to “more than four times a day.” To calculate the content of macronutrients and micronutrients for each food item, we used Spanish food composition databases [13,14].

The FFQ included the seven blue fish species and the 10 white fish species most frequently consumed in Galicia. Other seafood products included bivalves, crustaceans, and octopus, frequently consumed and with high content in n-3 LC-PUFA. We also assessed the intake of foods supplemented with n-3 LC-PUFA but not the use of specific n-3 LC-PUFA supplementation due to their insignificant consumption in our setting.

Furthermore, we asked questions about rhinitis symptoms, medical history, and questions on lifestyle variables that could be potential confounders of the relation between diet and AR.

## 2.7. Statistical analysis

The association of food items, macronutrients and micronutrients with AR occurrence was assessed using multivariate logistic regression models in which odds ratios (OR) and their corresponding 95 % confidence intervals (CI) were estimated. We presented the analysis per quartiles of exposure, or, when the distribution was excessively uneven, per tertiles. The analysis was controlled for the following potential confounders: age, sex, education level, history of asthma, history of dermatitis, familial history of allergy, body mass index, tobacco smoking (using WHO questionnaire) [26], and energy expenditure in Kcal/hour. Potential confounding variables were introduced successively in the model if they showed a p-value  $<0.2$  for the association with AR. In the final model, only those covariables that changed the estimate of the OR relating the main exposure to AR by at least 10 % were retained [27].

We adjusted the Odds Ratio of consumption of a specific type of fish by intake of fish of other species. We did not adjust for multiple testing following the recommendation of expert epidemiologists, as such an adjustment may introduce bias in the results instead of preventing it. Although this adjustment may reduce the type I error for null associations, it increases the type II error for those associations that are not null [28].

Furthermore, as in any epidemiologic study of a recurrent disease such as rhinitis, our study aimed at determining the role of exposure (in our case fish intake) in the occurrence of the *next episode* of the disease, not the *first* one. Indeed, it is not feasible to relate fish intake to the first occurrence *ever* of allergic rhinitis in the life of a subject, as the first bout of the disease probably appears early in life, likely before any fish is ever consumed.

Only cases and controls with complete information on the required variables were entered in the final analysis. All analyses were performed using the software SPSS version 18.0 and STATA version 12.

## 3. Results

### 3.1. Study population

Of 1200 invited subjects, 312 refused to participate. Finally, 411 cases and 477 controls fulfilled the inclusion criteria and were included in the study. The general characteristics of the study population are presented in Table 1. The mean age of the participants was 34.8 years, with a range of 16–81 years. Most cases (62.3 %) and controls (70.6 %) were females. There were more

**Table 1**  
General characteristics of cases and controls.

	Cases		Controls	
	No.	%	No.	%
<b>Sex</b>				
Women	256	62.3	337	70.6
Men	155	37.7	140	29.4
<b>Age (years)</b>				
$\leq 30$	190	46.1	171	35.9
31–40	122	29.7	166	34.8
41–50	64	15.6	80	16.8
51–60	22	5.4	36	7.5
$>60$	13	3.2	24	5.0
<b>Body Mass index (Kg/m<sup>2</sup>)</b>				
18.5–25	237	58.2	294	62.7
$<18.5$	12	2.9	18	3.8
25–30	125	30.6	101	21.5
$>30$	34	8.3	56	12.0
<b>Education</b>				
None or primary	119	29.7	81	17.7
Secondary	152	37.9	159	34.8
University	130	32.4	217	47.5
<b>History of asthma</b>				
Yes	255	62.0	19	4.7
No	156	38.0	386	95.3
<b>History of atopic dermatitis</b>				
Yes	94	22.9	18	4.4
No	317	77.1	387	95.6
<b>Familial history of allergic rhinitis</b>				
Yes	172	41.8	26	6.4
No	239	58.2	278	93.6
<b>Familial history of asthma or dermatitis</b>				
Yes	176	42.8	30	7.4
No	235	57.2	374	92.6
<b>Daily energy expenditure (Kcal/day)</b>				
$<1927$ (1st quartile)	78	19.1	140	29.7
1928–2424 (2nd quartile)	102	25.0	118	25.1
2425–2947 (3rd quartile)	116	28.4	113	24.0
$>2947$ (4th quartile)	112	27.5	100	21.2

**Table 2**  
Odds ratios (OR) and 95 % confidence intervals (CI) of fish consumption and allergic rhinitis.

Fish type	Intake	Median (serving/week)	Cases		Controls		Crude OR (95%CI)	Adjusted OR (95%CI) <sup>a</sup>	Adjusted OR (95% CI) <sup>b</sup>
			N	%	N	%			
All blue fish (except tuna)	1st quartile	0.0	138	33.58	61	12.79	Reference	Reference	Reference
	2nd quartile	1.0	111	27.01	142	29.77	0.35 (0.23–0.51)	0.46 (0.27–0.80)	0.45 (0.25–0.80)
	3rd quartile	2.0	94	22.87	147	30.82	0.28 (0.19–0.42)	0.30 (0.17–0.54)	0.35 (0.19–0.63)
	4th quartile	3.4	68	16.55	127	26.62	0.24 (0.16–0.36)	0.38 (0.20–0.70)	0.38 (0.20–0.73)
All blue fish (tuna included)	1st quartile	1.0	119	28.95	98	20.55	Reference	Reference	Reference
	2nd quartile	2.0	59	14.36	136	28.51	0.36 (0.24–0.54)	0.30 (0.16–0.53)	0.34 (0.19–0.63)
	3rd quartile	3.4	125	30.41	124	26.00	0.83 (0.58–1.20)	0.54 (0.31–0.92)	0.50 (0.28–0.88)
	4th quartile	6.0	108	26.28	119	24.95	0.75 (0.52–1.09)	0.75 (0.41–1.36)	0.62 (0.33–1.17)
Tuna	1st tertile	0.5	116	28.22	166	34.80	Reference	Reference	Reference
	2nd tertile	1.0	109	26.52	178	37.32	0.88 (0.63–1.23)	0.93 (0.57–1.51)	0.92 (0.54–1.54)
	3rd tertile	3.0	186	45.26	133	27.88	2.00 (1.45–2.77)	1.87 (1.11 – 3.16)	1.50 (0.83–2.70)
Salmon	1st tertile	0.0	217	52.80	170	35.64	Reference	Reference	Reference
	2nd tertile	0.5	131	31.87	211	44.23	0.49 (0.36–0.65)	0.46 (0.29–0.71)	0.62 (0.38–1.01)
	3rd tertile	1.0	63	15.33	96	20.13	0.51 (0.35–0.75)	0.72 (0.41–1.26)	0.64 (0.33–1.26)
Sardines	1st tertile	0.0	274	66.67	184	38.57	Reference	Reference	Reference
	2nd tertile	0.5	91	22.14	220	46.12	0.28 (0.20–0.38)	0.29 (0.18–0.46)	0.44 (0.26–0.75)
	3rd tertile	1.0	46	11.19	73	15.30	0.42 (0.28–0.64)	0.52 (0.28–0.97)	0.45 (0.22–0.94)
Blue jack mackerel	1st tertile	0.0	277	67.40	211	44.23	Reference	Reference	Reference
	2nd tertile	0.5	85	20.68	185	38.78	0.35 (0.26–0.48)	0.38 (0.24–0.60)	0.58 (0.34–0.99)
	3rd tertile	1.0	49	11.92	81	16.98	0.46 (0.31–0.69)	0.66 (0.36–1.23)	0.56 (0.28–1.13)
Anchovies (canned)	Infrequent	0.0	341	82.97	321	67.30	Reference	Reference	Reference
	Frequent	0.5	70	17.03	156	32.70	0.42 (0.31–0.58)	0.39 (0.24–0.63)	0.43 (0.25–0.75)
Eel, elver	Infrequent	0.0	352	85.64	383	80.29	Reference	Reference	Reference
	Frequent	0.5	59	14.36	94	19.71	0.68 (0.48–0.98)	0.93 (0.56–1.56)	1.05 (0.59–1.86)
White fish	1st tertile	0.5	87	21.17	227	47.59	Reference	Reference	Reference
	2nd tertile	1.0	114	27.74	130	27.25	2.29 (1.61–3.26)	2.76 (1.63–4.67)	2.80 (1.63–4.81)
	3rd tertile	3.0	210	51.09	120	25.16	4.57 (3.27–6.38)	5.49 (3.27 – 9.24)	5.10 (3.00–8.67)

<sup>a</sup> OR adjusted for sex, age, education, history of asthma, family history of asthma, and Kcal/day.

<sup>b</sup> OR adjusted for sex, age, education, history of asthma, family history of asthma, Kcal/day, and other fish species.

controls (47.5 %) with post-secondary education level than cases (32.4 %). A history of atopic dermatitis was absent in 77.1 % of cases and in 95.6 % of controls. A large proportion of the cases had a family member with AR (41.8 %) and/or asthma or dermatitis (42.8 %), while 62 % of cases reported a personal history of asthma. Overweight was more frequent in cases (30.6 %) than in controls (21.5 %). However, there were more obese controls (12.0 %) than obese cases (8.3 %). Finally, the daily caloric expenditure was higher in cases than in controls (Table 1). All these differences between cases and controls were taken into account in the analysis phase, and factors that were deemed confounders were adjusted for.

### 3.2. Blue fish

Intakes of more than one serving/week of blue fish, compared with an intake of 1 serving or less/week were associated with 43 %–68 % reduced odds of AR (Table 2). Compared with no intake, regular consumption of anchovy, blue jack mackerel, salmon, and sardine was also associated with lower odds of AR, ranging from 49 % to 69 %. On the contrary, a high intake (3 servings/week) of tuna was associated with an increase in the odds of AR of 87 %. Excluding tuna from the analysis of the consumption of any blue fish yielded a stronger magnitude of the protective association of blue fish with AR.

**Table 3**  
Odds ratios (OR) and 95 % confidence intervals (CI) of non-fish seafood type and allergic rhinitis.

Non-fish seafood type	Intake	Median (serving/week)	Cases		Controls		Crude OR (95%CI)	Adjusted OR (95%CI) <sup>a</sup>
			N	%	N	%		
Bivalve mollusks	1st tertile	0.0	140	34.06	131	27.46	Reference	Reference
	2nd tertile	0.5	166	40.39	244	51.15	0.64 (0.47–0.87)	0.62 (0.40–0.98)
	3rd tertile	1.0	105	25.55	102	21.38	0.96 (0.67–1.38)	1.28 (0.75–2.20)
Crustaceans	1st tertile	0.0	208	50.61	176	36.90	Reference	Reference
	2nd tertile	0.5	140	34.06	232	48.64	0.51 (0.38–0.68)	0.49 (0.32–0.74)
	3rd tertile	1.0	63	15.33	69	14.47	0.77 (0.52–1.15)	0.75 (0.42–1.36)
Octopus	1st tertile	0.0	150	36.50	138	28.93	Reference	Reference
	2nd tertile	0.5	179	43.55	244	51.15	0.68 (0.50–0.91)	0.56 (0.36–0.88)
	3rd tertile	1.0	82	19.95	95	19.92	0.79 (0.55–1.16)	0.80 (0.45–1.41)
Seafood (bivalve mollusks, crustaceans and octopus)	1st quartile	0.0	144	35.04	136	28.51	Reference	Reference
	2nd quartile	1.0	57	13.87	47	9.85	1.15 (0.73–1.80)	1.24 (0.63–2.42)
	3rd quartile	1.5	101	24.57	170	35.64	0.56 (0.40–0.79)	0.46 (0.28–0.77)
	4th quartile	2.9	109	26.52	124	26.00	0.83 (0.59–1.18)	1.05 (0.62–1.77)

<sup>a</sup> OR adjusted for sex, age, education, history of asthma, family history of asthma, and Kcal/day.

**Table 4**  
Odds ratios (OR) and 95 % confidence intervals (CI) of nutrient intake and allergic rhinitis.

Nutrients	Intake	Median (serving/week)	Cases		Controls		Crude OR (95%CI)	Adjusted OR (95%CI) <sup>a</sup>
			N	%	N	%		
Total fat	1st quartile	55.0	80	19.5	142	29.8	Reference	Reference
	2nd quartile	76.6	102	24.8	120	25.2	1.51 (1.03–2.2)	1.39 (0.83–2.33)
	3rd quartile	94.5	121	29.4	101	21.2	2.12 (1.45–3.11)	1.76 (1.02–3.02)
	4th quartile	135.0	108	26.3	114	23.9	1.68 (1.15–2.45)	0.96 (0.52–1.76)
Saturated fatty acid (SAFA)	1st quartile	15.4	83	20.2	139	29.1	Reference	Reference
	2nd quartile	22.6	103	25.1	119	25.0	1.44 (0.99–2.11)	1.21 (0.71–2.07)
	3rd quartile	29.9	117	28.5	105	22.0	1.86 (1.27–2.72)	1.64 (0.97–2.78)
	4th quartile	44.2	108	26.3	114	23.9	1.58 (1.08–2.31)	0.89 (0.49–1.61)
Mono-Unsaturated fatty acid (MUFA)	1st quartile	20.9	79	19.2	143	30.0	Reference	Reference
	2nd quartile	28.1	111	27.0	111	23.3	1.81 (1.23–2.64)	2.09 (1.24–3.53)
	3rd quartile	34.5	114	27.7	108	22.6	1.91 (1.31–2.79)	1.78 (1.03–3.06)
	4th quartile	50.1	107	26.0	115	24.1	1.68 (1.15–2.46)	0.98 (0.53–1.81)
Poly-Unsaturated Fatty acids (PUFA)	1st quartile	8.4	86	20.9	136	28.5	Reference	Reference
	2nd quartile	11.3	104	25.3	118	24.7	1.39 (0.95–2.03)	1.23 (0.73–2.08)
	3rd quartile	14.7	111	27.0	111	23.3	1.58 (1.08–2.31)	1.25 (0.74–2.13)
	4th quartile	21.1	110	26.8	112	23.5	1.55 (1.06–2.26)	0.96 (0.52–1.77)
n-6 PUFA	1st quartile	5.4	82	20.0	140	29.4	Reference	Reference
	2nd quartile	7.9	94	22.9	128	26.8	1.25 (0.85–1.83)	1.22 (0.72–2.05)
	3rd quartile	11.2	136	33.1	86	18.0	2.69 (1.83–3.96)	2.35 (1.37–4.03)
	4th quartile	16.2	99	24.1	123	25.8	1.37 (0.93–2.01)	0.78 (0.42–1.45)
n-3 PUFA	1st quartile	1.2	107	26.0	115	24.1	Reference	Reference
	2nd quartile	1.8	90	21.9	132	27.7	0.73 (0.50–1.06)	0.87 (0.52–1.45)
	3rd quartile	2.3	112	27.3	111	23.3	1.09 (0.75–1.58)	0.88 (0.52–1.49)
	4th quartile	3.7	102	24.8	119	25.0	0.91 (0.62–1.32)	0.59 (0.33–1.07)
n-6/n-3	1st quartile	2.8	79	19.2	143	30.0	Reference	Reference
	2nd quartile	4.0	97	23.6	125	26.2	1.40 (0.95–2.05)	1.35 (0.79–2.31)
	3rd quartile	5.2	116	28.2	106	22.2	1.98 (1.35–2.89)	1.75 (1.01–3.04)
	4th quartile	7.4	119	29.0	103	21.6	2.09 (1.42–3.06)	1.79 (1.03–3.13)
Linoleic Acid (LA) 18:2n-6	1st quartile	4.9	80	19.5	142	29.8	Reference	Reference
	2nd quartile	6.8	109	26.5	113	23.7	1.71 (1.17–2.50)	1.50 (0.89–2.51)
	3rd quartile	9.1	115	28.0	107	22.4	1.91 (1.30–2.78)	1.59 (0.93–2.72)
	4th quartile	12.9	107	26.0	115	24.1	1.65 (1.12–2.41)	1.02 (0.57–1.85)
Alpha-Linolenic Acid (ALA) 18:3n-3	1st quartile	0.6	92	22.4	130	27.3	Reference	Reference
	2nd quartile	0.8	99	24.1	123	25.8	1.13 (0.78–1.65)	0.94 (0.56–1.58)
	3rd quartile	1.0	109	26.5	113	23.7	1.36 (0.93–1.98)	0.93 (0.55–1.58)
	4th quartile	1.5	111	27.0	111	23.3	1.41 (0.97–2.05)	0.85 (0.48–1.52)
Stearidonic Acid (EA) 18:4n-3	1st quartile	0.01	144	35.0	77	16.1	Reference	Reference
	2nd quartile	0.02	99	24.0	124	26.0	0.37 (0.25–0.55)	0.52 (0.31–0.87)
	3rd quartile	0.04	84	20.4	137	28.7	0.29 (0.20–0.44)	0.26 (0.15–0.46)
	4th quartile	0.08	84	20.4	139	29.1	0.30 (0.20–0.44)	0.42 (0.24–0.74)
Arachidonic Acid (AA) 20:4n-6	1st quartile	0.1	79	19.2	143	30.0	Reference	Reference
	2nd quartile	0.2	98	23.8	124	26.0	1.43 (0.97–2.09)	1.81 (1.06–3.07)
	3rd quartile	0.3	138	33.6	84	17.6	2.97 (2.02–4.37)	2.51 (1.44–4.37)
	4th quartile	0.4	96	23.4	126	26.4	1.37 (0.94–2.02)	1.24 (0.69–2.23)
Eicosapent-aeoic acid (EPA) 20:5n-3	1st quartile	0.1	134	32.6	88	18.5	Reference	Reference
	2nd quartile	0.2	97	23.6	124	26.0	0.48 (0.33–0.71)	0.61 (0.37–1.05)
	3rd quartile	0.3	88	21.4	135	28.3	0.41 (0.28–0.61)	0.49 (0.29–0.84)
	4th quartile	0.5	92	22.4	130	27.3	0.45 (0.31–0.66)	0.45 (0.25–0.80)
Docosapen-taenoic acid (DPA) 22:5n-3	1st quartile	0.03	122	29.7	99	20.8	Reference	Reference
	2nd quartile	0.06	93	22.6	132	27.7	0.58 (0.40–0.85)	0.57 (0.34–0.96)
	3rd quartile	0.08	100	24.3	120	25.2	0.69 (0.47–1.01)	0.69 (0.41–1.16)
	4th quartile	0.14	96	23.4	126	26.4	0.61 (0.42–0.89)	0.54 (0.31–0.96)
Docosahe-xaenoic acid (DHA) 22:6n-3	1st quartile	0.2	126	30.7	96	20.1	Reference	Reference
	2nd quartile	0.4	98	23.8	124	26.0	0.58 (0.40–0.85)	0.62 (0.37–1.05)
	3rd quartile	0.5	85	20.7	140	29.4	0.45 (0.31–0.66)	0.48 (0.28–0.81)
	4th quartile	0.9	102	24.8	117	24.5	0.65 (0.44–0.94)	0.60 (0.34–1.06)

<sup>a</sup> OR adjusted for sex, age, history of asthma, history of dermatitis, family history of rhinitis, and Kcal/day.

### 3.3. White fish

Consuming three servings/week of white fish, compared to low intake, was associated with an OR of AR of 5.49 (95 % CI: 3.27–9.24) (Table 2).

### 3.4. Non-fish seafood

The most commonly used types of seafood other than fish in our settings are bivalve mollusks (mussels, clams, razor clams, oysters, cockles, and scallops), crustacean (crab, spider crab, lobster, prawns, langoustines) and octopus. Compared to no intake, an

intake of 0.5 servings/week of each type of those seafoods was associated with 38 %–51 % lower odds of AR (Table 3) The combined analysis of bivalve mollusks, crustaceans and octopus showed 54 % lower odds of AR from the consumption of 1.5 servings/week of these products when compared to no intake (Table 3). The association was stronger when the analysis was restricted to men (OR = 0.21; 95%CI: 0.09–0.51) (data not shown).

### 3.5. Fat type

Compared with low intake, intake of the third quartile of total fat was associated with an increased odds of AR (OR = 1.76, 95%CI:

**Table 5**  
Odds ratios (OR) and 95 % confidence intervals (CI) of protein intake and allergic rhinitis.

Proteins	Intake	Median (serving/week)	Cases		Controls		Crude OR (95% CI)	Adjusted OR (95% CI) <sup>a</sup>
			N	%	N	%		
Total Protein	1st quartile	66.7	64	15.6	158	33.1	Reference	Reference
	2nd quartile	90.1	97	23.6	125	26.2	1.91 (1.29–2.83)	2.00 (1.15–3.49)
	3rd quartile	114.7	126	30.7	97	20.3	3.21 (2.16–4.75)	2.42 (1.35–4.32)
	4th quartile	151.4	124	30.2	97	20.3	3.15 (2.12–4.67)	2.13 (1.11–4.11)
Animal Protein	1st quartile	44.2	67	16.3	155	32.5	Reference	Reference
	2nd quartile	63.7	105	25.6	117	24.5	2.07 (1.41–3.06)	2.75 (1.56–4.83)
	3rd quartile	81.5	120	29.2	102	21.4	2.72 (1.84–4.01)	2.23 (1.24–4.01)
	4th quartile	114.4	119	29.0	103	21.6	2.67 (1.81–3.94)	2.01 (1.06–3.80)
Vegetal Protein	1st quartile	21.5	65	15.8	157	32.9	Reference	Reference
	2nd quartile	31.6	103	25.1	119	25.0	2.09 (1.41–3.09)	2.01 (1.15–3.54)
	3rd quartile	39.4	124	30.2	98	20.6	3.05 (2.06–4.52)	2.39 (1.34–4.24)
	4th quartile	52.6	119	29.0	103	21.6	2.79 (1.88–4.12)	2.01 (1.06–3.81)

<sup>a</sup> OR adjusted for sex, age, history of asthma, history of dermatitis, family history of rhinitis and Kcal/day.

1.02–3.02). The other quartiles did not reach statistical significance (Table 4).

The analysis by fat type revealed a significant association of the second (OR = 2.09, 95%CI: 1.24–3.53) and third (OR = 1.78, 95%CI: 1.03–3.06) quartiles of intake of MUFA with AR, while no association between total PUFA or total SAFA intake and AR was observed (Table 3). Stratifying the analysis by PUFA types showed that the third quartile intake of n-6 PUFA was associated with higher odds of AR, while n-3 PUFA, linoleic acid (LA) 18:2n-6, and alpha-linolenic acid (ALA) 18:3n-3 did not show any association with AR (Table 4).

Other subtype analyses showed increased odds of AR for n-6:n-3 PUFA and arachidonic acid (AA), and decreased odds for eicosapentaenoic acid (EPA), docosapentaenoic acid (DPA) and docosahexaenoic acid (DHA).

### 3.6. Proteins

Overall, any total protein intake higher than the lowest quartile was associated with approximately a doubling in the odds of AR. The magnitude of the association remained unaltered when the analysis was stratified by protein origin, vegetal or animal (Table 5).

## 4. Discussion

Our results show that not all fish species present the same association with AR, as some species –blue fish–decrease the odds of the disease, while others –white fish–have an opposite role. Likewise, the association and its magnitude vary between nutrients and levels of intake. Our results are consistent with the hypothesis of a protective effect on AR of a high n-3 PUFA intake and with that of an increase in the risk of AR for high n-6 PUFA and protein intakes.

For proteins, a possible mechanism has been hypothesized, involving certain polycyclic compounds formed during cooking [29,30], that, after ingestion, interfere with the  $\beta$  adrenergic receptors of the respiratory epithelium [21,29].

The antagonistic effects of the proteins and the different PUFAs clearly explain the relation between the different fish and sea products regarding AR. Blue fish is rich in fatty acids EA, EPA, DPA and DHA, all of which have an anti-inflammatory effect [31]. On the contrary, white fish, rich in proteins and poor in PUFA [31], would

increase the risk of AR. The effect of tuna, which, as a blue fish, is expected to decrease the risk of AR, does not contradict the previous explanation since tuna fatty acid composition varies widely according to the mode of preparation and consumption (fresh or canned) [32]. Canned tuna, unlike fresh tuna, is very poor in n-3 LC PUFA, a substance with strong anti-inflammatory property, but very rich in n-6 PUFA, a substance that favors inflammation. Moreover, fresh tuna, when manipulated [33], undergoes a rapid transformation mediated by bacteria, in which histamine, a strong mediator of allergic reactions, is produced.

Our findings confirm those of several previous studies [10,12,15,34], but disagree with others [16]. In the prospective study by Nagel [12], a similar result was obtained for fatty acids ALA and EPA, but not for AA and DHA nor for the ratio n-6/n-3. In the cross-sectional study by Trak-Fellermeier [11], the authors reported results similar to ours in women for total PUFA, LA and n-6/n-3 ratio, but not for ALA and AA. In the cross-sectional study by Hoff [13], the authors found a similar association of AA and ALA with AR but not of the other LC-PUFA. Four other Japanese cross-sectional studies agreed partially with our results [10,15,17,22].

The dietary patterns influence patients' inflammatory response [35]. While linoleic acid (LA) generates derivatives with pro-inflammatory effects, n-3 LC-PUFA exerts an anti-inflammatory response by suppressing interleukins [9]. The modification of dietary patterns through time has led to an increase in the n-6/n-3 ratio from a value of 1 in the diet adopted by humans in the past to a value ranging between 15 and 30 in the modern diet [36]. The n-3 and n-6 PUFAs are found mainly in fish and seafood [37,38]. They are considered essential Fatty Acids and their consumption is recommended because humans lack the  $\Delta 12$ - and  $\Delta 15$ -desaturase enzymes for the synthesis of the shorter chain precursors  $\alpha$ -LA (18:3n-3) and linolenic acid (LA, 18:2n-6) [39].

A certain degree of error is possible in our measurement of food intake (exposure), but it is very likely that any exposure misclassification, if it happened, was non-differential with respect to disease status. Should misclassification occur, our results would be biased towards the null value and the true effect would be underestimated. Likewise, despite the relatively high figures of sensitivity and specificity of our diagnosis of AR shown by our validation study, 0.74 and 0.92 respectively, misclassification of the outcome cannot

be ruled out as symptoms of rhinitis are often mistaken with upper respiratory tract infections such as common cold or sinusitis [4]. Again, in this case, potential disease misclassification would occur independently of exposure (diet) and, again, the effect we measured would be underestimated.

One possible limitation of our study is the existence, as in any observational study, of residual confounding, i.e. confounding due to unmeasured factors. Although efforts were made to adjust our analysis for several potential confounders, using a strict and pre-established modeling procedure, we cannot rule out the presence of residual confounding.

In our study we used a four-point cutoff score to ascertain AR from reported criteria; however, our main results did not change substantially when we used other cutoff points.

Recall bias could induce cases to recall symptoms and diet exposure better than controls. However, in our setting, such a bias is highly unlikely to occur as both cases and controls were unaware of their disease status before the end of the study.

In conclusion, different fish species, sea products, and their fat and protein contents are associated with AR occurrence. The direction of the association varies between the different fish products and its magnitude is dose-dependent. It would be of special interest to investigate whether the effect of tuna intake on AR is related to the way this fish is prepared and consumed. Further research, preferably of longitudinal design and in different settings and populations, is required to confirm our findings.

### Contribution of each author

CR, JS, and BT designed and conducted the research; CR, NM, FJGB, and BT analyzed and interpreted data; and NM wrote the paper. All authors read and approved the final manuscript and accepted responsibility for its content.

### Data availability statement

Data are available upon reasonable request from B-T ([bahitakkouche@usc.es](mailto:bahitakkouche@usc.es)).

### Funding of the research

This work was funded by a grant from Carlos III Health Institute (PI10/01295), Madrid, Spain, and FEDER.

### Conflict of interest

The authors have no conflict of interest to declare.

### References

- [1] Savoure M, Bousquet J, Jaakkola JJK, Jaakkola MS, Jacquemin B, Nadif R. Worldwide prevalence of rhinitis in adults: a review of definitions and temporal evolution. *Clin Transl Allergy* 2022;12(3):e12130.
- [2] Kritikos V, Price D, Papi A, Infantino A, Stallberg B, Ryan D, et al. The burden of self-reported rhinitis and associated risk for exacerbations with moderate-severe asthma in primary care patients. *J Asthma Allergy* 2020;13:415–28.
- [3] Brozek JL, Bousquet J, Agache I, Agarwal A, Bachert C, Bosnic-Anticevich S, et al. Allergic rhinitis and its impact on asthma (ARIA) guidelines-2016 revision. *J Allergy Clin Immunol* 2017;140(4):950–8.
- [4] Gonzalez-Barcala FJ, Martinez-Torres AE, Mendez-Brea P, Garcia-Marcos L. With the torch in the mist of the united airway disease: atopic march and other arguments in the search for evidence. *Arch Bronconeumol* 2022;58(5):386–7.
- [5] Roland LT, Wise SK, Wang H, Zhang P, Mehta C, Levy JM. The cost of rhinitis in the United States: a national insurance claims analysis. *Int Forum Allergy Rhinol* 2021;11(5):946–8.
- [6] Bousquet J, Van Cauwenberge P, Khaltaev N, Aria Workshop G, World Health O. Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol* 2001;108(5 Suppl):S147–334.
- [7] Gonzalez Barcala F, Acevedo-Prado A, Seoane-Pillado A, López-Silvarrey A, Pérttega S, Salgado F, et al. The impact of the mediterranean diet on rhinitis prevalence. *Eur Respir J* 2022;60.
- [8] Antonogeorgos G, Mandrapyllia M, Liakou E, Koutsokera A, Drakontaeidis P, Thanasia M, et al. Hierarchical analysis of mediterranean dietary pattern on atopic diseases' prevalence in adolescence: the Greek global asthma network study. *Allergol Immunopathol* 2022;50(5):114–20.
- [9] Simopoulos AP. Evolutionary aspects of the dietary omega-6:omega-3 fatty acid ratio: medical implications. *World Rev Nutr Diet* 2009;100:1–21.
- [10] Magnusson J, Kull I, Westman M, Hakansson N, Wolk A, Melen E, et al. Fish and polyunsaturated fat intake and development of allergic and nonallergic rhinitis. *J Allergy Clin Immunol* 2015;136(5):1247–53. e1–2.
- [11] Trak-Fellermeier MA, Brasche S, Winkler G, Koletzko B, Heinrich J. Food and fatty acid intake and atopic disease in adults. *Eur Respir J* 2004;23(4):575–82.
- [12] Nagel G, Nieters A, Becker N, Linseisen J. The influence of the dietary intake of fatty acids and antioxidants on hay fever in adults. *Allergy* 2003;58(12):1277–84.
- [13] Hoff S, Seiler H, Heinrich J, Kompauer I, Nieters A, Becker N, et al. Allergic sensitisation and allergic rhinitis are associated with n-3 polyunsaturated fatty acids in the diet and in red blood cell membranes. *Eur J Clin Nutr* 2005;59(9):1071–80.
- [14] Andreasen K, Ponsonby AL, Dwyer T, Kemp A, Dear K, Cochrane J, et al. A differing pattern of association between dietary fish and allergen-specific subgroups of atopy. *Allergy* 2005;60(5):671–7.
- [15] Miyake Y, Tanaka K, Sasaki S, Arakawa M. Polyunsaturated fatty acid intake and prevalence of eczema and rhinoconjunctivitis in Japanese children: the ryukyus child health study. *BMC Public Health* 2011;11:358.
- [16] Miyake Y, Tanaka K, Okubo H, Sasaki S, Arakawa M. Dietary meat and fat intake and prevalence of rhinoconjunctivitis in pregnant Japanese women: baseline data from the kyushu Okinawa maternal and child health study. *Nutr J* 2012;11:19.
- [17] Kremmyda LS, Vlachava M, Noakes PS, Diaper ND, Miles EA, Calder PC. Atopy risk in infants and children in relation to early exposure to fish, oily fish, or long-chain omega-3 fatty acids: a systematic review. *Clin Rev Allergy Immunol* 2011;41(1):36–66.
- [18] Hamazaki K, Tsuchida A, Takamori A, Tanaka T, Ito M, Inadera H, et al. Dietary intake of fish and omega-3 polyunsaturated fatty acids and physician-diagnosed allergy in Japanese population: the Japan environment and Children's study. *Nutrition* 2019;61:194–201.
- [19] Kocatepe D, Turan H. Proximate and fatty acid composition of some commercially important fish species from the Sinop region of the Black Sea. *Lipids* 2012;47(6):635–41.
- [20] Bauchau V, Durham SR. Prevalence and rate of diagnosis of allergic rhinitis in Europe. *Eur Respir J* 2004;24(5):758–64.
- [21] Bousquet J, Khaltaev N, Cruz AA, Denburg J, Fokkens WJ, Togias A, et al. Allergic rhinitis and its impact on asthma (ARIA) 2008 update (in collaboration with the world health organization, GA(2)LEN and AllerGen). *Allergy* 2008;63(Suppl 86):8–160.
- [22] Wallace DV, Dykewicz MS, Bernstein DI, Blessing-Moore J, Cox L, Khan DA, et al. The diagnosis and management of rhinitis: an updated practice parameter. *J Allergy Clin Immunol* 2008;122(2 Suppl):S1–84.
- [23] Mastin T. Recognizing and treating non-infectious rhinitis. *J Am Acad Nurse Pract* 2003;15(9):398–409.
- [24] Bousquet J, Schunemann HJ, Samolinski B, Demoly P, Baena-Cagnani CE, Bachert C, et al. Allergic rhinitis and its impact on asthma (ARIA): achievements in 10 years and future needs. *J Allergy Clin Immunol* 2012;130(5):1049–62.
- [25] Martín-Moreno JM, Boyle P, Gorgojo L, Maisonneuve P, Fernandez-Rodriguez JC, Salvini S, et al. Development and validation of a food frequency questionnaire in Spain. *Int J Epidemiol* 1993;22(3):512–9.
- [26] Vilain C. The evaluation and monitoring of public action on tobacco. In: *Smoke-free Europe 3*. Copenhagen: WHO Regional Office for Europe; 1987.
- [27] Greenland S, Robins JM. Confounding and misclassification. *Am J Epidemiol* 1985;122(3):495–506.
- [28] Rothman KJ. No adjustments are needed for multiple comparisons. *Epidemiology* 1990;1(1):43–6.
- [29] Factor P, Akhmedov AT, McDonald JD, Qu A, Wu J, Jiang H, et al. Polycyclic aromatic hydrocarbons impair function of beta2-adrenergic receptors in airway epithelial and smooth muscle cells. *Am J Respir Cell Mol Biol* 2011;45(5):1045–9.
- [30] Rosenkranz RR, Rosenkranz SK, Neessen KJ. Dietary factors associated with lifetime asthma or hayfever diagnosis in Australian middle-aged and older adults: a cross-sectional study. *Nutr J* 2012;11:84.
- [31] Mataix Verdú José. *Tabla de composición de alimentos [Food composition table]*. 4th ed. Spain: University of Granada; 2003.
- [32] Ministerio de Agricultura Pesca y Alimentación [Ministry of Agriculture Fisheries and Food]. *Informe del Consumo de alimentación en España 2021*. 2022. Madrid.
- [33] FAO/WHO [Food and Agriculture Organization of the United Nations/World Health Organization]. *Public Health Risks of Histamine and other Biogenic Amines from Fish and Fishery Products*. Meeting report. 2013:1–126
- [34] Wakai K, Okamoto K, Tamakoshi A, Lin Y, Nakayama T, Ohno Y. Seasonal allergic rhinoconjunctivitis and fatty acid intake: a cross-sectional study in Japan. *Ann Epidemiol* 2001;11(1):59–64.

- [35] Koelman L, Egea Rodrigues C, Aleksandrova K. Effects of dietary patterns on biomarkers of inflammation and immune responses: a systematic review and meta-analysis of randomized controlled trials. *Adv Nutr* 2022;13(1):101–15.
- [36] Gomez Candela C, Bermejo Lopez LM, Loria Kohen V. Importance of a balanced omega 6/omega 3 ratio for the maintenance of health: nutritional recommendations. *Nutr Hosp* 2011;26(2):323–9.
- [37] Adamkova V, Kacer P, Mraz J, Suchanek P, Pickova J, Kralova Lesna I, et al. The consumption of the carp meat and plasma lipids in secondary prevention in the heart ischemic disease patients. *Neuroendocrinol Lett* 2011;32(Suppl 2):17–20.
- [38] Lund EK. Health benefits of seafood; is it just the fatty acids? *Food Chem* 2013;140(3):413–20.
- [39] Adkins Y, Kelley DS. Mechanisms underlying the cardioprotective effects of omega-3 polyunsaturated fatty acids. *J Nutr Biochem* 2010;21(9):781–92.