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Dietary intake of fish and ω-3 polyunsaturated fatty acids and physician-diagnosed allergy in Japanese population: The Japan Environment and Children's Study

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ABSTRACT

Objective: Emerging evidence from epidemiologic studies and clinical trials indicates that ω-3 polyunsaturated fatty acids (PUFAs) may have a preventive or therapeutic effect on allergy, although the results remain controversial. The aim of this study was to investigate the association between intake of fish and ω-3 PUFAs with risk for lifetime prevalence of physician-diagnosed allergy in a Japanese population.
Methods: Study participants were 78 621 pregnant women and 42 831 male partners from The Japan Environment and Children's Study. History of physician-diagnosed allergy (asthma, allergic rhinitis/pollinosis, allergic conjunctivitis, or atopic dermatitis) was determined by self-administered questionnaire survey. Dietary intake of fish and ω-3 PUFAs was estimated using a food frequency questionnaire.
Results: Contrary to our hypothesis, an increased risk for allergy was found by multivariable logistic regression in females, especially in allergic rhinitis/pollinosis, allergic conjunctivitis, or atopic dermatitis for fish intake and in allergic rhinitis/pollinosis or allergic conjunctivitis for ω-3 PUFAs. As for male partners, risk for allergic rhinitis/pollinosis or atopic dermatitis was increased for both fish and ω-3 PUFA intake. No statistically significant results were observed for the risk for asthma in either women or men.
Conclusion: Fish and ω-3 PUFA intake were associated with increased risk for some allergic diseases. Further research is warranted to confirm these findings in individuals with high fish consumption.

Introduction

The incidence of allergy has increased globally in recent decades and is potentially linked to development of public hygiene and changes in lifestyle [1]. From the viewpoint of changing lifestyles, nutrient intake is an interesting topic, especially intake of the long-chain (LC) ω-3 polyunsaturated fatty acids (PUFAs), such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Associations between ω-3 PUFA intake during pregnancy and childhood allergic disease have been the subject of many studies following the suggestion that dietary ω-3 PUFAs in early life may influence immune system and immune cell function [2]. Of three recent meta-analyses, one showed ω-3 LC-PUFAs in the maternal diet had beneficial effects on childhood allergic disease outcomes [3], whereas the other two showed no such beneficial effects [4,5].

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The mechanism underlying the association between PUFAs and allergy is attributed to the involvement of the proinflammatory eicosanoids prostaglandin E2 (PGE2) and leukotriene B4 (LTB4), which are metabolites of ω-6 PUFAs, and of the less inflammatory eicosanoid LTB5, which is a metabolite of ω-3 PUFAs [2]. LTB5 is 10- to 100-fold less potent as a neutrophil chemotactic agent than LTB4 [2]. Increased ω-3 PUFA consumption leads to an elevated proportion of these fatty acids in the cell membranes at the expense of ω-6 PUFAs [2]. This change in balance not only reduces the production of eicosanoids from ω-6 PUFAs, but also increases the production of ω-3 PUFA-derived eicosanoids [2]. In addition, DHA and EPA are metabolized to pro-resolving mediators, including resolvins, protectins, and maresins [6]. All of these pathways eventually confer anti-inflammatory properties [2].

The results of cross-sectional studies examining the association of dietary ω-3 PUFA consumption and allergy in Japan are controversial. Some studies have reported the beneficial effects of dietary ω-3 PUFAs, fish intake, or a combination [7–9] on allergy, whereas others have shown no effects [10–12] or even a potentially increased allergy risk with fish intake [13,14]. These mixed and inconclusive results may be attributed to differences in sample size, participant background, allergy, or dietary assessment tools, suggesting that further research is required.

Japanese consume large amounts of fish compared with Western populations. For example, the average fish intake is 69.8 g/d (488.6 g/wk) among men and 59.4 g/d (415.8 g/wk) among women in Japan [15] and 179.2 g/wk and 138.6 g/wk, respectively, in the United States [16]. The recent Dietary Guidelines for Americans (2015–2020) recommend consumption of >227g/wk of fish [17]. However, ~80% to 90% of Americans did not meet the recommendations for seafood when needs were estimated based on energy requirements [16].

According to a recent National Health and Nutrition Examination Survey [15,18], fish consumption is on the decline over the past decade in Japan, especially among younger generations. We hypothesized that young adults might benefit from taking ω-3 PUFAs for prevention of allergy. To test this hypothesis, in this study we investigated the association between dietary fish and ω-3 PUFA intake and physician-diagnosed allergy in Japanese women and their male partners, using data from the Japan Environment and Children's Study (JECS).

Materials and methods

Study population

The methods of the JECS have been described in detail elsewhere [19,20]. Briefly, JECS is a nationwide government-funded birth cohort study that is evaluating the effects of various environmental factors on children's health and development. The pregnant women participating in JECS were recruited from 15 areas in Japan between January 2011 and March 2014 [19,20]. The present study is based on the jecs-ag-20160424 data set that was released in June 2016 and the allbirth_revice001_ver001 data set that was released in October 2016. The full data set is for 103 099 maternal registrations, 5645 of which we excluded because of multiple registration in the study (Fig. 1). We also excluded data for 29 pregnancies in women who withdrew from the study for personal reasons and for women who gave incomplete answers on the questionnaires, leaving 78 621 for final analysis. Similarly, 2230 of the 51 909 male partners registered in the data set were excluded because of multiple entries for different pregnancies, leaving 49 679 participants. We excluded an additional 9 individuals who withdrew and 6839 who gave incomplete answers on the questionnaires. This left data for 42 831 male partners for the final analysis (Fig. 1). The study protocol was approved by the Ministry of the Environment's Institutional Review Board on Epidemiological Studies and by the ethics committees of all participating institutions. Written informed consent was obtained from all participating women and their male partners.

Measurements

A self-administered questionnaire was administered to the pregnant women on two occasions (early and mid-late pregnancy) to collect data on demographics, medical and obstetric history, physical and mental health, lifestyle, occupation, and socioeconomic status during pregnancy [21]. Information also was obtained from the medical records on gravidity, related complications, parity, maternal anthropometry, and other factors during early pregnancy [21]. A similar self-administered questionnaire was administered on one occasion to the male partners of the pregnant women during the pregnancy (no specific time designated).

Dietary fish and ω-3 PUFA intake was determined via a food frequency questionnaire (FFQ), which is semiquantitative and has been validated for use in large-scale Japanese epidemiologic studies [22,23]. Pregnant women were asked how often they consumed each food type during early pregnancy (also covering dietary intake in the previous year, i.e., the periconception period) and during mid-late pregnancy (covering dietary intake after learning of the pregnancy). In the present study, we analyzed only the data set gathered in early pregnancy from them. Male partners completed the FFQ at the same time they completed the self-administered questionnaire (no specific time designated). The standard portion size for each food type was categorized as small (50% smaller than standard), medium (same as standard), or large (50% larger than standard). For each of the 21 items of fish or shellfish, the standard portion size (with the approximate equivalent size in grams) is as follows: slice of salted fish (70 g); one whole dried fish (50 g); quarter of a can of tuna (20 g); slice of salmon or trout (70 g); 4 sashimi slices of bonito or tuna (60 g); 4 sashimi slices of Japanese amberjack (60 g); half slice of cod or flatfish (40 g); slice of sea bream (70 g); one whole horse mackerel or sardine (80 g); one whole saury or mackerel (80 g); 2 tablespoons of small dried fish (10 g); one-fourth of a clutch of salted roe (20 g); half skewer of eel (50 g); 3 sashimi slices of squid (50 g); one-third of an octopus tentacle (50 g); 2 Chinese white shrimps (40 g); 10 shucked clams (20 g); 10 shucked pond-snails (20 g); and fish paste products comprising one-sixth of *chikuwa* (20 g), 2 slices of *kamaboko* (20 g), and one-fourth of *satsuma-age* (20 g).

The nine frequency categories for each item were <1 time/mo, 1–3 times/mo, 1–2 times/wk, 3–4 times/wk, 5–6 times/wk, daily, 2–3 times/d, 4–6 times/d, and ≥7 times/d. Daily intake of fish (g/d) was calculated by multiplying frequency of consumption by standard portion size for each of the 21 fish or shellfish items listed. α-Linolenic acid intake was calculated largely from cooking oil [24]. To calculate the daily intake of ω-3 PUFAs, intake of the subtypes alpha-linolenic acid, EPA, docosapentaenoic acid, and DHA was calculated using a fatty acid composition table of Japanese foods [25] and summed (data for the individual subtypes of fatty acids were not included in the JECS data set).

Data on allergies were collected in early pregnancy by self-administered questionnaire (multiple choice). Participants responded to the question, "From birth, have you ever been diagnosed by a physician?" for 13 disease sections (each section concerning between 3 and 14 specific diseases). In the section "Allergies and otolaryngologic disease," we decided to analyze data for the four top allergic diseases: allergic rhinitis or pollinosis; atopic dermatitis; asthma; and allergic conjunctivitis. We defined participants as having "any allergy" if they were diagnosed with any of these four allergic diseases.

Statistical analysis

Data are expressed as the means ± SD or median unless stated otherwise. To estimate the risk for allergic diseases for different levels of fish intake and ω-3 PUFA intake, we categorized the participants according to quintiles. We then performed logistic regression analysis to calculate odds ratios (ORs) and 95% confidence intervals (CIs). Tests for trend involved assigning categorical numbers to quintile distributions for fish intake and ω-3 PUFA intake and evaluating these as continuous variables. All analysis was adjusted for age, energy intake, previous deliveries, pre-pregnancy body mass index, highest educational level, annual household income, alcohol intake, smoking status, physical activity, and employment status for women. For male partners, previous deliveries and physical activity were excluded from the adjustment because there were no data on the relationship between the risk for asthma and parity for male partners (but such data are available for female partners [26]), and physical activity was not measured for male partners. The details of re-categorization of choices in each factors were described in the previous study [27]. Two-sided *P* values of <0.05 were considered statistically significant. Data were analyzed using SAS version 9.4 software (SAS Institute Inc., Cary, NC, USA).

Results

Participant characteristics

Table 1 and Supplementary Table 1 show maternal characteristics according to quintile for fish intake and ω-3 PUFA intake, respectively. Women reporting higher fish intake, when compared with those reporting low fish intake, were found to have a higher energy intake and to be slightly older. They also showed a tendency to be multiparous, have higher levels of education and annual

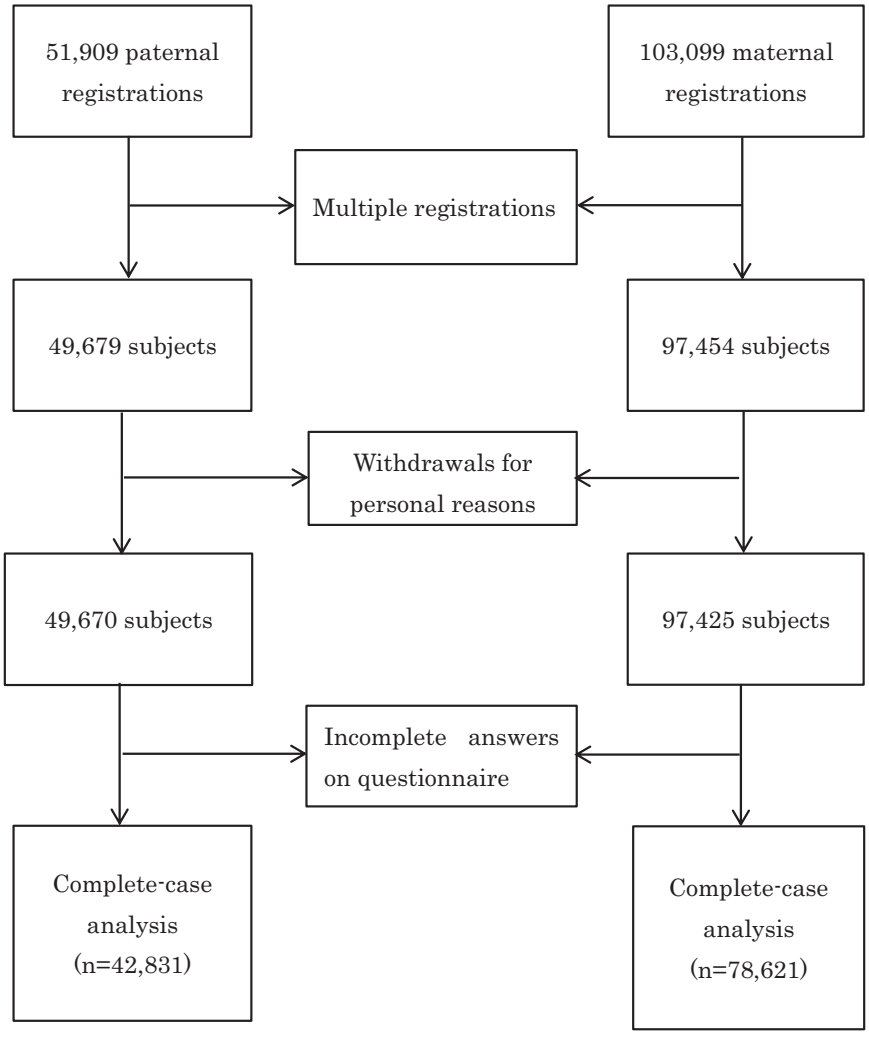

Fig. 1. Flow diagram of the recruitment and exclusion process for pregnant women and their male partners in this study.

household income, and to be a current drinker, more physically active, and a non-smoker. Male partners had highly similar associations for dietary fish intake (Table 2) and ω-3 PUFA intake (Supplementary Table 2) during their partner's pregnancy.

Lifetime prevalence of allergic diseases

The lifetime prevalence of any allergy was 49.4% and 40.2% in women and men, respectively. The lifetime prevalence of asthma, allergic rhinitis/pollinosis, allergic conjunctivitis, and atopic dermatitis was 10.9%, 36.4%, 10.2%, and 16% in women and 10.9%, 30.7%, 4.4%, and 11.4% in men, respectively.

Multivariable logistic regression for allergic diseases

Table 3 shows the multivariable ORs for allergic diseases and 95% CIs according to quintile for fish and ω-3 PUFA intake in women (n = 78 621). Fish intake was positively associated with the risk for any allergy, and ORs for the second to fifth quintiles were significantly higher. Some increased risks were observed for allergic rhinitis/pollinosis, allergic conjunctivitis, and atopic dermatitis but not asthma. The highest OR was found in the fifth quintile for fish intake for allergic conjunctivitis (OR, 1.14; 95% CI 1.06–1.24). Similar results were observed in ω-3 PUFA intake in women, but the risk for atopic dermatitis was attenuated compared with that for fish intake. Very similar results were found for men (n = 42 831), except that the ORs were higher for atopic dermatitis and lower for allergic conjunctivitis. The highest OR was found in the fourth quintile for ω-3 PUFA intake for atopic dermatitis (OR, 1.24; 95% CI 1.12–1.38; Table 4). No statistically significant results were observed for the risk for asthma in either women or men. Supplementary Tables 3 and 4 show the multivariable ORs for allergic diseases and 95% CIs according to quintile for ω-6 PUFA intake in women and men, respectively. The results were similar to those of ω-3 PUFA intake (Tables 3 and 4), respectively.

Discussion

In contrast to our hypothesis, fish intake was associated with increased risk for allergic rhinitis/pollinosis, allergic conjunctivitis, or atopic dermatitis in women and risk for allergic rhinitis/pollinosis and atopic dermatitis in men. Similar associations also were observed for ω-3 and ω-6 PUFA intake. To our knowledge, this is the first nationwide, community-based research in Japan to report on the association of fish and ω-3 PUFA intake and allergy risk.

The lifetime prevalence of 10.9% for female asthma in this study was higher than that in a previous study conducted in Osaka City (2.1% for those treated with medication at some time during the

Table 1
Maternal characteristics according to quintile for fish intake in the first trimester and preceding 1-y perinatal period (N = 78 621)

	Quintile for fish intake				
	1 (low)	2	3	4	5 (high)
Median intake of fish*, g/d	7.3	20.3	31.7	45.9	76.0
Median intake of energy*	1377	1526	1658	1810	2173
Age at baseline questionnaire, y	29.8	30.7	31.2	31.5	31.6
Previous deliveries, n (%)					
Nullipara	8337 (53)	7032 (45.2)	6483 (40.7)	6108 (38.9)	5835 (37.1)
Multipara	7404 (47)	8529 (54.8)	9435 (59.3)	9581 (61.1)	9877 (62.9)
Prepregnancy BMI, kg/m^2 (%)					
<18.5	2625 (16.7)	2602 (16.7)	2485 (15.6)	2370 (15.1)	2398 (15.3)
18.5 to <25	11 433 (72.6)	11, 452 (73.6)	11 804 (74.2)	11 707 (74.6)	11 450 (72.8)
≥25	1683 (10.7)	1507 (9.7)	1629 (10.2)	1612 (10.3)	1864 (11.9)
Highest level of education (%)					
Junior high school or high school	6663 (42.3)	5678 (36.5)	5179 (32.5)	4873 (31.1)	4988 (31.8)
Technical junior college, technical/vocational college, or associate degree	6303 (40)	6473 (41.6)	6857 (43.1)	6873 (43.8)	6847 (43.6)
Bachelor's degree, postgraduate degree	2775 (17.6)	3410 (21.9)	3882 (24.4)	3943 (25.1)	3877 (24.7)
Annual household income, JPY (%)					
<4 million	7477 (47.5)	6369 (40.9)	5937 (37.3)	5574 (35.5)	5834 (37.1)
4–6 million	4814 (30.6)	5127 (33.0)	5419 (34)	5473 (34.9)	5162 (32.9)
>6 million	3450 (21.9)	4065 (26.1)	4562 (28.7)	4642 (29.6)	4716 (30)
Alcohol intake					
Never	5689 (36.1)	5424 (34.9)	5444 (34.2)	5168 (32.9)	5097 (32.4)
Ex	8727 (55.5)	8576 (55.1)	8744 (54.9)	8748 (55.8)	8850 (56.4)
Current	1325 (8.4)	1561 (10)	1730 (10.9)	1773 (11.3)	1765 (11.2)
Smoking status (%)					
Never	8613 (54.7)	8997 (57.8)	9682 (60.8)	9542 (60.8)	9332 (59.4)
Quit before learning of pregnancy	3545 (22.5)	3747 (24.1)	3656 (23)	3746 (23.9)	3821 (24.3)
Quit after learning of pregnancy	2625 (16.7)	2111 (13.6)	1937 (12.2)	1809 (11.5)	1844 (11.7)
Currently smoking	958 (6.1)	706 (4.5)	643 (4)	592 (3.8)	715 (4.6)
Median physical activity (METS•min/day)	113	113	118	125	153
Employed, n (%)	10 484 (66.6)	9830 (63.2)	9869 (62)	9727 (62)	9869 (62.8)

BMI, body mass index; METS, metabolic equivalent; PUFA, polyunsaturated fatty acids.
*Includes during the year preceding questionnaire administration (i.e., perinatal period).

previous 12 mo and 4.7% for asthma after age 18 y) [9]. This is reasonable because the present study concerned any physician-diagnosed asthma at any age and, in general, asthma is known to be outgrown by adolescence [28]. The lifetime prevalence of the specified allergic diseases—allergic rhinitis/pollinosis, allergic conjunctivitis, and atopic dermatitis—in the present study differed only slightly from that

Table 2
Paternal characteristics according to quintile for fish intake during female partner's pregnancy (N = 42 831)

	Quintile for fish intake				
	1 (low)	2	3	4	5 (high)
Median intake of fish*, g/d	4.7	20.7	35.5	53	90
Median intake of energy*	1749	1918	2058	2234	2722
Age at baseline questionnaire, y	31.8	32.5	33.1	33.3	33.4
BMI, kg/m^2 (%)					
<18.5	363 (4.3)	351 (4.1)	304 (3.5)	256 (3)	247 (2.9)
18.5 to <25	6022 (71)	6090 (70.3)	6061 (70.7)	5932 (69.4)	5586 (65.2)
≥25	2096 (24.7)	2213 (25.6)	2217 (25.8)	2364 (27.6)	2729 (31.9)
Educational background (%)					
Junior high school or high school	4191 (49.4)	3660 (42.2)	3230 (37.6)	3191 (37.3)	3359 (39.3)
Technical junior college, technical/vocational college, or associate Degree	1970 (23.2)	2099(24.3)	2065 (24.1)	1992 (23.3)	2015 (23.5)
Bachelor's degree, postgraduate degree	2320 (27.4)	2895 (33.5)	3287 (38.3)	3369 (39.4)	3188 (37.2)
Annual family income, JPY (%)					
<4 million	3858 (45.5)	3501 (40.5)	3118 (36.3)	2944 (34.4)	3162 (36.9)
4–6 million	2731 (32.2)	2919 (33.7)	2965 (34.6)	2976 (34.8)	2899(33.9)
>6 million	1892 (22.3)	2234 (25.8)	2499 (29.1)	2632 (30.8)	2501 (29.2)
Alcohol intake (%)					
Never	2215 (26.1)	2007 (23.2)	1748 (20.4)	1604 (18.8)	1483 (17.3)
Ex	364 (4.3)	329 (3.8)	297 (3.5)	269 (3.2)	270 (3.2)
Current	5902 (69.6)	6318 (73)	6537(76.1)	6679 (78.0)	6809 (79.5)
Smoking status (%)					
Never	2262 (26.7)	2585 (29.9)	2646 (30.8)	2646 (30.9)	2493 (29.1)
Quit before learning of pregnancy	1824 (21.5)	2033 (23.5)	2138 (24.9)	2070 (24.2)	2115 (24.7)
Quit after learning of pregnancy	463 (5.5)	430 (5)	417 (4.9)	383 (4.5)	409 (4.8)
Currently smoking	3932 (46.3)	3606 (41.7)	3381 (39.4)	3453 (40.4)	3545 (41.4)
Employed, n (%)	8386 (98.9)	8563 (99)	8500 (99)	8486 (99.2)	8475 (99)

BMI, body mass index.
*Includes during the year preceding questionnaire administration (i.e., perinatal period).

Table 3
Odds ratios (95% confidence intervals) for maternal allergy according to quintile for fish and ω-3 PUFA intake (N = 78 621)

	Quintile for fish intake					
	1 (low)	2	3	4	5 (high)	P_{trend}
Median intake of fish*, g/d	7.3	20.3	31.7	45.9	76.0	
All participants, n	15 741	15 561	15 918	15 689	15 712	
Any of four allergies						
Cases, n	7409	7612	7969	7975	7889	
Crude odds ratio	1.00	**1.08 (1.03–1.13)**	**1.13 (1.08–1.18)**	**1.16 (1.11–1.22)**	**1.13 (1.08–1.19)**	**<0.0001**
Adjusted odds ratio†	1.00	**1.05 (1.00–1.10)**	**1.08 (1.04–1.13)**	**1.11 (1.06–1.16)**	**1.07 (1.02–1.12)**	**0.0007**
Asthma						
Cases, n	1767	1611	1678	1746	1800	
Crude odds ratio	1.00	**0.91 (0.85–0.98)**	0.93 (0.87–1.00)	0.99 (0.92–1.06)	1.02 (0.95–1.10)	0.12
Adjusted odds ratio	1.00	0.94 (0.87–1.01)	0.97 (0.90–1.04)	1.03 (0.96–1.11)	1.05 (0.97–1.13)	**0.03**
Allergic rhinitis or pollinosis						
Cases, n	5401	5561	5905	5915	5891	
Crude odds ratio	1.00	**1.06 (1.02–1.12)**	**1.13 (1.08–1.18)**	**1.16 (1.11–1.21)**	**1.15 (1.10–1.20)**	**<0.0001**
Adjusted odds ratio	1.00	1.02 (0.98–1.07)	**1.06 (1.01–1.11)**	**1.08 (1.03–1.13)**	**1.06 (1.01–1.11)**	**0.005**
Allergic conjunctivitis						
Cases, n	1443	1547	1653	1653	1700	
Crude odds ratio	1.00	**1.09 (1.01–1.18)**	**1.15 (1.07–1.24)**	**1.17 (1.08–1.26)**	**1.20 (1.12–1.29)**	**<0.0001**
Adjusted odds ratio	1.00	1.06 (0.98–1.14)	**1.09 (1.01–1.18)**	**1.10 (1.02–1.19)**	**1.14 (1.06–1.24)**	**0.0008**
Atopic dermatitis						
Cases, n	2439	2505	2537	2579	2546	
Crude odds ratio	1.00	1.05 (0.98–1.11)	1.03 (0.97–1.10)	**1.07 (1.01–1.14)**	1.05 (0.99–1.12)	0.06
Adjusted odds ratio	1.00	1.05 (0.99–1.12)	1.05 (0.98–1.11)	**1.09 (1.02–1.16)**	**1.07 (1.00–1.14)**	**0.02**
	Quintile for ω−3 PUFA intake					
	1 (low)	2	3	4	5 (high)	P_{trend}
Median intake of ω-3 PUF*, g/d	0.91	1.37	1.75	2.21	3.13	
All participants, n	15 694	15 734	15 637	15 867	15 689	
Any of four allergies						
Cases, n	7428	7744	7819	8025	7837	
Crude odds ratio	1.00	**1.08 (1.03–1.13)**	**1.11 (1.06–1.16)**	**1.14 (1.09–1.19)**	**1.11 (1.06–1.16)**	**<0.0001**
Adjusted odds ratio	1.00	1.04 (1.00–1.09)	**1.06 (1.01–1.11)**	**1.07 (1.02–1.13)**	1.03 (0.97–1.09)	0.11
Asthma						
Cases, n	1797	1661	1645	1743	1756	
Crude odds ratio	1.00	**0.91 (0.85–0.98)**	**0.91 (0.85–0.98)**	0.95 (0.89–1.02)	0.97 (0.91–1.05)	0.9
Adjusted odds ratio	1.00	0.94 (0.87–1.01)	0.93 (0.86–1.00)	0.97 (0.90–1.04)	0.95 (0.87–1.04)	0.4
Allergic rhinitis or pollinosis						
Cases, n	5371	5668	5806	5988	5840	
Crude odds ratio	1.00	**1.08 (1.03–1.13)**	**1.14 (1.08–1.19)**	**1.16 (1.11–1.22)**	**1.14 (1.09–1.19)**	**<0.0001**
Adjusted odds ratio	1.00	1.04 (0.99–1.09)	**1.07 (1.02–1.12)**	**1.08 (1.03–1.14)**	1.04 (0.98–1.10)	**0.04**
Allergic conjunctivitis						
Cases, n	1455	1573	1650	1704	1614	
Crude odds ratio	1.00	**1.09 (1.01–1.17)**	**1.15 (1.07–1.24)**	**1.18 (1.09–1.27)**	**1.12 (1.04–1.21)**	**0.0003**
Adjusted odds ratio	1.00	1.05 (0.98–1.14)	**1.11 (1.02–1.20)**	**1.13 (1.04–1.22)**	1.09 (0.99–1.20)	**0.02**
Atopic dermatitis						
Cases, n	2468	2499	2572	2554	2513	
Crude odds ratio	1.00	1.01 (0.95–1.07)	1.06 (0.99–1.12)	1.03 (0.97–1.09)	1.02 (0.96–1.09)	0.4
Adjusted odds ratio	1.00	1.01 (0.95–1.08)	1.05 (0.99–1.12)	1.03 (0.96–1.10)	1.03 (0.95–1.11)	0.4

BMI, body mass index.
Bold type indicates statistical significance ($P < 0.05$).
*Intake was determined by responses to the food frequency questionnaire for the preceding 1-y perinatal period (from questionnaire administration in the first trimester).
†Adjusted for age, energy intake, number of previous deliveries (nullipara or multipara), pre-pregnancy BMI (<18.5, ≤18.5 to <25, or ≥25), highest level of education, annual household income, alcohol intake, smoking status, physical activity, and employment status.

reported in previous studies [7,8,10,11], likely because of differences in disease classification, survey timing, or the study population.

Among the previous cross-sectional studies conducted in Japan [7–14], the following considerations should be kept in mind. Those individuals in whom fish intake was found to have a negative effect (an increased risk for allergy) were children aged 6 to 15 years [13,14]; the remaining participants were young adults or adults [7–11] (except for one study involving preschool children [12]). As for differences in sample size, those studies found that increased risk was clearly larger—>20 000 [13,14] versus 1000 to 2000 individuals [7–12]—indicating that increased risk did not occur by chance because of a small sample size. Considering cross-sectional studies conducted in Western countries that involve >1000 participants, one study showed a beneficial effect of ω-3 PUFAs [29] and four others showed no such benefit [30–33]; none of the five studies showed a negative effect (increased risk) from fish or ω-3 PUFA intake [29–33]. Outside of Japan, only one study has been conducted in an Asian country where fish consumption is high, namely Taiwan. In that population-based, cross-sectional survey (1166 adolescents 13–17 y of age), univariate analysis revealed that higher frequency of oily fish intake was associated with asthma, although the association disappeared on multivariate logistic regression analysis [34]. It appears that those studies conducted in countries with high fish intake (>227 g or 2 servings/wk of fish) showed not only a beneficial effect of dietary fish or ω-3 PUFA consumption on allergy, but also a negative effect (increased risk). More evidence from interventional studies is needed to clarify these findings.

Table 4
Odds ratios (95% confidence intervals) for paternal allergy according to quintile for fish and ω-3 PUFA intake (N = 42 831)

	Quintile for fish intake					
	1 (low)	2	3	4	5 (high)	P_{trend}
Median intake of fish*, g/d	4.7	20.7	35.5	53	90	
All participants, n	8481	8654	8582	8552	8562	
Any of four allergies						
Cases, n	3397	3651	3702	3676	3571	
Crude odds ratio	1.00	**1.09 (1.03–1.16)**	**1.14 (1.07–1.21)**	**1.13 (1.06–1.20)**	**1.07 (1.01–1.14)**	**0.02**
Adjusted odds ratio†	1.00	**1.07 (1.00–1.14)**	**1.10 (1.03–1.17)**	**1.09 (1.03–1.16)**	1.05 (0.99–1.13)	0.08
Asthma						
Cases, n	914	977	919	915	942	
Crude odds ratio	1.00	1.05 (0.96–1.16)	0.99 (0.90–1.09)	0.99 (0.90–1.09)	1.02 (0.93–1.13)	0.89
Adjusted odds ratio	1.00	1.07 (0.97–1.17)	1.02 (0.92–1.12)	1.02 (0.92–1.12)	1.04 (0.94–1.15)	0.79
Allergic rhinitis or pollinosis						
Cases, n	2412	2671	2765	2714	2578	
Crude odds ratio	1.00	**1.12 (1.05–1.20)**	**1.20 (1.12–1.28)**	**1.17 (1.10–1.25)**	**1.08 (1.01–1.16)**	**0.008**
Adjusted odds ratio	1.00	**1.08 (1.01–1.16)**	**1.13 (1.06–1.21)**	**1.11 (1.03–1.18)**	1.05 (0.98–1.12)	0.14
Allergic conjunctivitis						
Cases, n	353	361	420	373	368	
Crude odds ratio	1.00	1.00 (0.86–1.16)	**1.18 (1.03–1.37)**	1.05 (0.90–1.22)	1.03 (0.89–1.20)	0.51
Adjusted odds ratio	1.00	0.97 (0.84–1.13)	1.13 (0.98–1.31)	1.00 (0.86–1.17)	1.01 (0.86–1.18)	0.80
Atopic dermatitis						
Cases, n	886	993	985	1,008	994	
Crude odds ratio	1.00	**1.11 (1.01–1.22)**	**1.11 (1.01–1.22)**	**1.15 (1.04–1.26)**	**1.13 (1.02–1.24)**	**0.02**
Adjusted odds ratio	1.00	**1.11 (1.01–1.23)**	**1.12 (1.02–1.24)**	**1.16 (1.05–1.27)**	**1.15 (1.04–1.28)**	**0.006**
	Quintile for ω-3 PUFA intake					
	1 (low)	2	3	4	5 (high)	P_{trend}
Median intake of ω-3 PUFA*, g/d	0.89	1.40	1.83	2.36	3.48	
All subjects, n	8541	8557	8578	8554	8601	
Any of four allergies						
Cases, n	3342	3638	3670	3719	3628	
Crude odds ratio	1.00	**1.15 (1.08–1.22)**	**1.16 (1.09–1.24)**	**1.20 (1.13–1.27)**	**1.13 (1.07–1.21)**	**<0.0001**
Adjusted odds ratio	1.00	**1.12 (1.05–1.19)**	**1.13 (1.06–1.21)**	**1.18 (1.10–1.25)**	**1.14 (1.06–1.23)**	**<0.0001**
Asthma						
Cases, n	896	942	923	925	981	
Crude odds ratio	1.00	1.06 (0.96–1.16)	1.03 (0.93–1.13)	1.03 (0.94–1.14)	1.10 (1.00–1.21)	0.12
Adjusted odds ratio	1.00	1.06 (0.96–1.17)	1.03 (0.94–1.14)	1.04 (0.94–1.15)	1.09 (0.97–1.22)	0.26
Allergic rhinitis or pollinosis						
Cases, n	6134	5917	5858	5813	5969	
Crude odds ratio	1.00	**1.14 (1.06–1.21)**	**1.18 (1.11–1.26)**	**1.20 (1.13–1.28)**	**1.12 (1.05–1.20)**	**0.0001**
Adjusted odds ratio	1.00	**1.10 (1.03–1.18)**	**1.15 (1.07–1.23)**	**1.18 (1.10–1.26)**	**1.14 (1.06–1.24)**	**0.0001**
Allergic conjunctivitis						
Cases, n	332	374	385	407	377	
Crude odds ratio	1.00	1.13 (0.97–1.31)	**1.16 (1.00–1.35)**	**1.24 (1.07–1.43)**	1.13 (0.97–1.32)	**0.049**
Adjusted odds ratio	1.00	1.10 (0.94–1.28)	1.12 (0.96–1.31)	**1.21 (1.03–1.41)**	1.14 (0.95–1.36)	0.07
Atopic dermatitis						
Cases, n	845	981	1,019	1,034	987	
Crude odds ratio	1.00	**1.18 (1.07–1.30)**	**1.23 (1.11–1.35)**	**1.25 (1.14–1.38)**	**1.18 (1.07–1.30)**	**0.0005**
Adjusted odds ratio	1.00	**1.17 (1.06–1.29)**	**1.21 (1.10–1.34)**	**1.24 (1.12–1.38)**	**1.18 (1.05–1.32)**	**0.002**

BMI, body mass index.
Bold type indicates statistical significance ($P < 0.05$).
*Intake was determined by responses to the food frequency questionnaire in the preceding 1-y perinatal period (from questionnaire administration).
†Adjusted for age, energy intake, BMI (<18.5, ≤18.5 to <25, or ≥25), highest level of education, annual household income, alcohol intake, smoking status, and employment status.

Although the results of previous meta-analyses are controversial [3–5], none of the studies showed a deteriorative effect of fish or ω-3 PUFA consumption. The question then arises as to why allergy risks for fish or ω-3 PUFA consumption were found in the present study. One reason might be the presence of harmful environmental contaminants such as methylmercury, polychlorinated biphenyls (PCBs), and dioxins. Gascon's systematic review of epidemiologic research suggests that early life exposure to persistent organic pollutants can adversely influence development of the immune and respiratory systems [35]. In fact, a cross-sectional study in Japan revealed significant positive correlations between the frequency of fish and shellfish intake and some congers of dioxins and polychlorinated biphenyls in blood [36]. Moreover, the correlations were much stronger between plasma DHA and these congers [36]. A longitudinal study in Japan revealed that prenatal exposure to dioxins may modify the immune responses of offspring and result in increased allergy risk among school-age children [37]. An observational study in Korea showed that low-level mercury exposure was associated with asthma and blood profile changes in school-age children [38]. Although hair mercury levels are correlated with fish consumption in pregnant women [39] and young adults [40] in Japan, there is no association of hair mercury levels in either mothers or children with the risk for wheeze or eczema in children in Japan [41].

Another plausible reason why the present study found allergy risks for fish or ω-3 PUFA consumption might be reverse causation. The Ministry of Health, Labour and Welfare first included ω-3 PUFAs in the Dietary Reference Intakes for Japanese in 2005 [42] as

a nutritional index for achieving "tentative dietary goals for preventing lifestyle related diseases." Since then, Japanese people have come to recognize ω-3 PUFAs as a functional nutrient with anti-atherosclerotic, anti-inflammatory, and other beneficial properties [43], and many now make concerted efforts to increase their intake. Accordingly, people with a history of allergy might be more health conscious and consume more fish.

The anti-inflammatory property of ω-3 PUFA is thought to be preventive and have therapeutic effects on allergy [2]. The ω-3–derived metabolites are precursors for the anti-inflammatory eicosanoids, whereas the ω-6 PUFAs can be precursors for the proinflammatory eicosanoids [43]. In addition to these eicosanoids, there is other evidence showing that metabolites from EPA and DHA themselves have both anti-inflammatory and proresolution activities. Among these metabolites, the D- and E-series resolvins are metabolized from DHA and EPA, respectively, protectin is metabolized from DHA, and lipoxin is metabolized from arachidonic acid (AA) [44]. Recently, a comprehensive lipidomics analysis of oxygenated metabolites of AA, EPA, and DHA produced by mast cells revealed that certain epoxygenated EPA and DHA metabolites (ω-3 epoxides) unexpectedly enhanced mast cell activation and anaphylaxis [45]. These particular ω-3 epoxides might account for the higher risk for allergy that we found in this study for those who ate more fish or more ω-3 PUFAs. This area of research is still in its infancy, and the association between ω-3 epoxides and its effect requires further study.

As mentioned previously, ω-6 PUFAs have the potential to exert proinflammatory effects [43]. The effects of eicosanoids derived from AA, namely PGE2 and LTB4 have been studied widely. LTB4 is a leukotriene that plays numerous roles in inflammation including its function as a potent eicosanoid lipid chemoattractant [46]. It is produced rapidly by activated cells of innate immunity such as neutrophils, macrophages, and mast cells [46]. The association elevated LTB4 levels with disease activity and treatment response has been described in various allergic conditions [46]. From these mechanisms, we expected to find an opposite effect (higher risks) of ω-6 PUFA consumption compared with ω-3 PUFA consumption (protective). However, the results of ω-6 PUFA intake (Supplementary Tables 3 and 4) were almost the same as those of ω-3 PUFA intake (Tables 3 and 4). We do not have a clear explanation for these results, but the difficulties in evaluating the consumption of AA from the FFQ (ω-6 PUFA intake was assessed largely using cooking oil, and the kind of cooking oil was not queried in the FFQ [24]) might have obscured the relationship between the consumption of AA and the risk for allergy. To resolve this issue, direct measurement of ω-6 PUFA level from tissue may be needed.

The strengths of the present study are its large sample size—in fact, the largest size ever in Japan for this population (pregnant women and their male partner)—and the administration of comprehensive and standardized questionnaires (including the FFQ), which enabled us to assess a variety of characteristics and increase our ability to adjust for potential confounding factors.

The study limitations include its observational nature, which may have led to unmeasured residual factors confounding the results; for instance, fish consumption may serve as a proxy for a healthy lifestyle in general [47]. Second, the data set did not include the ω-3 PUFA subtypes for detailed analysis. Third, we also needed to exclude a large number of individuals with incomplete questionnaire responders (~20 000 pregnant women and 7000 male partners), which may have introduced a degree of selection bias. Fourth, both dietary intake and allergy outcomes were determined by questionnaire survey. Hence, there is a potential for both exposure and outcome misclassification. Fifth, owing to the cross-sectional nature of the study, a cause-and-effect relationship cannot be clarified.

Conclusion

Both fish intake and ω-3 PUFA intake were associated with increased allergy risk for some allergic diseases. Further research is warranted to confirm our findings in individuals with high fish consumption.

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Supplementary data

Supplementary data related to this article can be found at doi:10.1016/j.nut.2018.11.010.

Appendix

The following are the members of the Japan Environment and Children's Study (JECS) (principal investigator, Toshihiro Kawamoto) as of 2018: Yukihiro Ohya (National Center for Child Health and Development, Tokyo, Japan), Reiko Kishi (Hokkaido University, Sapporo, Japan), Nobuo Yaegashi (Tohoku University, Sendai, Japan), Koichi Hashimoto (Fukushima Medical University, Fukushima, Japan), Chisato Mori (Chiba University, Chiba, Japan), Shuichi Ito (Yokohama City University, Yokohama, Japan), Zentaro Yamagata (University of Yamanashi, Chuo, Japan), Hidekuni Inadera (University of Toyama, Toyama, Japan), Michihiro Kamijima (Nagoya City University, Nagoya, Japan), Takeo Nakayama (Kyoto University, Kyoto, Japan), Hiroyasu Iso (Osaka University, Suita, Japan), Masayuki Shima (Hyogo College of Medicine, Nishinomiya, Japan), Yasuaki Hirooka (Tottori University, Yonago, Japan), Narufumi Suganuma (Kochi University, Nankoku, Japan), Koichi Kusuhara (University of Occupational and Environmental Health, Kitakyushu, Japan), and Takahiko Katoh (Kumamoto University, Kumamoto, Japan).

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