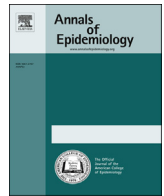




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Maternal fat intake during pregnancy and wheeze and eczema in Japanese infants: the Kyushu Okinawa Maternal and Child Health Study

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ABSTRACT

Purpose: This cohort study examined the relationship between maternal intake of individual fatty acids, meat, and fish during pregnancy and the risk of wheeze and eczema in children aged 23–29 months because epidemiologic evidence on this topic is inconclusive.

Methods: Subjects were 1354 Japanese mother-child pairs. Data on maternal intake during pregnancy were assessed with a validated diet history questionnaire. Data on symptoms of wheeze and eczema were based on criteria of the International Study of Asthma and Allergies in Childhood.

Results: Significant inverse exposure-response relationships were observed between maternal intake of eicosapentaenoic acid (EPA) and EPA plus docosahexaenoic acid (DHA) during pregnancy and infantile wheeze although the adjusted odds ratios between extreme quartiles fell just short of the significance level. No such inverse relationships were detected for infantile eczema. Maternal intake of total fat, saturated fatty acids, monounsaturated fatty acids, total n-3 polyunsaturated fatty acids (PUFA), α -linolenic acid, DHA, total n-6 PUFA, linoleic acid, arachidonic acid, cholesterol, fish, and meat and the ratio of n-3 to n-6 PUFA consumption were not significantly related to infantile wheeze or eczema.

Conclusions: Higher maternal intake of EPA and EPA plus DHA during pregnancy may reduce the risk of infantile wheeze.

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Introduction

It has been suggested that maternal diet during pregnancy may impact fetal immune development and subsequently alter the allergic responses of the child [1,2]. One hypothesis proposes that higher intake of n-6 polyunsaturated fatty acids (PUFA) might increase the risk of allergic disorders, whereas higher intake of n-3 PUFA may be protective against allergic disorders [3]. Significant positive relationships were observed between maternal intake levels of margarine and vegetable oils rich in n-6 PUFA during pregnancy and infantile eczema at 2 years of age in a cohort study in Germany [4]. Several epidemiologic studies have found significant inverse associations between maternal fish intake rich in n-3 PUFA during pregnancy and the following outcomes: eczema in infants aged 2 years [4], childhood asthma during the first 5 years of life [5],

eczema in 5-year-old children [6], childhood eczema at age 1 year and atopic wheeze at age 6 years [7], infantile eczema in the first year of life [8], and asthma at 18 months and history of asthma in 7-year-old children [9]; in two studies, however, no inverse associations were detected between maternal fish intake during pregnancy and childhood wheeze or asthma from 1 to 8 years of age [10] or between maternal fish intake during pregnancy and wheeze in infants aged 16–24 months [11].

Epidemiologic information regarding maternal PUFA intake during pregnancy and childhood allergic disorders has been sparse to date. In a Japanese cohort study, higher maternal intake of α -linolenic acid and docosahexaenoic acid (DHA) during pregnancy was significantly associated with a reduced risk of infantile wheeze but not eczema, whereas higher maternal intake of n-6 PUFA, especially linoleic acid, during pregnancy was significantly related to an increased risk of infantile eczema but not wheeze at 16–24 months of age [11]. A cohort study in Finland showed significant inverse associations between maternal intake of total n-3 PUFA and α -linolenic acid, but not DHA or eicosapentaenoic acid (EPA), during pregnancy and asthma, as well as a significant positive relationship

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between maternal arachidonic acid intake during pregnancy and asthma and also a significant inverse association between maternal saturated fatty acid intake and asthma in children aged 5 years with a high or moderate genetic risk of type 1 diabetes [12]. Because epidemiologic evidence on this topic is inconclusive, further evidence is required.

Here, we examined the relationship between maternal intake of individual fatty acids, meat, and fish during pregnancy and the risk of wheeze and eczema in Japanese children aged 23–29 months using data from the Kyushu Okinawa Maternal and Child Health Study (KOMCHS).

Methods

Study population

The KOMCHS is a prospective prebirth cohort study that investigates risk and preventive factors for maternal and child health problems. Details of the baseline survey of the KOMCHS have been described elsewhere [13]. Eligible women were those who became pregnant while living in one of seven prefectures on Kyushu Island in southern Japan, with a total population of approximately 13.26 million, or in Okinawa Prefecture, an island chain in the southwest of Japan, with a total population of nearly 1.37 million. Between April 2007 and March 2008, we requested that 423 obstetric hospitals in the above-mentioned eight prefectures provide as many pregnant women as possible with a set of leaflets explaining the KOMCHS, an application form to participate in the study, and a self-addressed and stamped return envelope. Pregnant women who were willing to participate in the study returned the application form to the data management center. In total, 1757 pregnant women between the fifth and 39th weeks of pregnancy gave their full informed consent in writing to participate in the KOMCHS and completed the baseline survey. Of the 1757 women, 1590 (90.5%), 1527 (86.9%), 1430 (81.4%), and 1362 (77.5%) mother-child pairs participated in the second (after delivery), third (around 4 months postpartum), fourth (around 12 months postpartum), and fifth (around 24 months postpartum) surveys, respectively. Excluded were five pairs who did not participate in the fifth survey at 23–29 months postpartum, one pair with missing data on the date of the fifth survey, one pair with missing data on household income, and one pair with missing data on the child's gender, leaving 1354 pairs for the current analysis. The ethics committee of the Faculty of Medicine, Fukuoka University approved the KOMCHS.

Measurements

In each survey, a self-administered questionnaire was used. Participants filled out questionnaires and mailed the answered questionnaires to the data management center at the time of each survey. Research technicians completed missing or illogical data by telephone interview.

The first part of the questionnaire at baseline elicited information on maternal age; gestation; region of residence; number of children; maternal and paternal education; household income; and maternal and paternal history of asthma, atopic eczema, and allergic rhinitis. Maternal or paternal history of asthma, atopic eczema, and allergic rhinitis was defined as positive if the respective parent had been diagnosed by a physician as having any of these allergic disorders.

The second part of the first questionnaire was a semiquantitative, comprehensive diet history questionnaire (DHQ) that assessed dietary habits during the preceding month. Estimates of daily intake of foods (total of 150 foods), energy, and selected nutrients were calculated using an *ad hoc* computer algorithm for

the DHQ based on the Standard Tables of Food Composition in Japan [14]. Information on dietary supplements was not used in the calculation of dietary intake because of the lack of a reliable composition table in Japan. The correlation coefficients between nutrient intake estimated in the DHQ and that observed in a 3-day dietary record were 0.75, 0.50, 0.37, and 0.49 for saturated fatty acids, monounsaturated fatty acids, polyunsaturated fatty acids, and cholesterol, respectively, in 47 women [15]. A strong positive correlation was also observed between marine-origin n-3 polyunsaturated fatty acid intake estimated by the DHQ and the corresponding concentration in the serum phospholipid fraction in 44 women ($r = 0.69$) [16]. Energy-adjusted intake by the residual method was used for the analyses [17].

A questionnaire in the second survey asked about the baby's sex, birth weight, and date of birth, and maternal smoking during pregnancy. Questionnaires in the third and fourth surveys inquired about household smoking and breastfeeding duration. A questionnaire in the fifth survey included questions on symptoms of wheeze and eczema based on the International Study of Asthma and Allergies in Childhood [18,19]. Wheeze was defined as present if the mother answered "yes" to the question "Has your child had wheezing or whistling in the chest in the last 12 months?". For eczema, affirmative answers to the following three questions were required: "Has your child ever had an itchy rash which was coming and going for at least 6 months?", "Has your child had this itchy rash at any time in the last 12 months?", and "Has this itchy rash at any time affected any of the following places: the folds of the elbows, behind the knees, in front of the ankles, under the buttocks, or around the neck, ears, or eyes?"

Statistical analysis

Intake of each of the dietary factors under study was categorized at quartile points on the basis of its distribution among 1354 mothers. Maternal age; gestation at baseline; region of residence at baseline; number of children at baseline; maternal and paternal education; family income; maternal and paternal history of asthma, atopic eczema, and allergic rhinitis; baby's birth weight; baby's sex; maternal smoking during pregnancy; household smoking during the first year of life; and breastfeeding duration were selected *a priori* as potential confounding factors.

Logistic regression analysis was performed to estimate crude odds ratios (ORs) and their 95% confidence intervals (CIs) for wheeze and eczema according to the quartiles of the dietary factors under investigation, with the lowest quartile as the reference. Multiple logistic regression analysis was used to adjust for potential confounding factors. The trend of association was assessed by a logistic regression model in which the median value in each quartile of the exposure variables was assigned as the representative score. Two-sided values of P less than .05 were considered statistically significant. All computations were performed using the SAS software package version 9.2 (SAS Institute, Inc., Cary, NC).

Results

In the fifth survey, the prevalence values of wheeze and eczema were 27.6% and 16.9%, respectively, among 1354 children. The mean maternal age at baseline was 31.5 years (Table 1). About 45% of mothers and 55% of fathers had received 15 years or longer of education. The mothers of 8% of the children had smoked during pregnancy. About 89% of the children had been breastfed for 6 months or longer. Maternal mean daily energy-adjusted intake of EPA and DHA was 0.17 and 0.29 g, respectively (Table 2).

Compared with the sum of maternal intake of EPA and DHA during pregnancy in the lowest quartile, maternal intake in the

Table 1
Distribution of selected characteristics of 1354 parent-child pairs

Variable	n (%)
Baseline characteristics	
Maternal age, y, mean $\pm$ SD	31.5 $\pm$ 4.1
Gestation, wk, mean $\pm$ SD	18.2 $\pm$ 5.4
Region of residence	
Fukuoka Prefecture	783 (57.8)
Prefecture on Kyushu Island other than Fukuoka	442 (32.6)
Okinawa Prefecture	129 (9.5)
Number of living children already born to same mother	
0	541 (40.0)
1	543 (40.1)
≥ 2	270 (19.9)
Maternal education, y	
<13	293 (21.6)
13–14	455 (33.6)
≥ 15	606 (44.8)
Paternal education, y	
<13	409 (30.2)
13–14	198 (14.6)
≥ 15	747 (55.2)
Household income, Japanese yen/y	
<4,000,000	454 (33.5)
4,000,000–5,999,999	497 (36.7)
$\geq 6,000,000$	403 (29.8)
Maternal history of asthma	179 (13.2)
Maternal history of atopic eczema	246 (18.2)
Maternal history of allergic rhinitis	564 (41.7)
Paternal history of asthma	147 (10.9)
Paternal history of atopic eczema	133 (9.8)
Paternal history of allergic rhinitis	374 (27.6)
Characteristics at the postnatal assessment	
Birth weight, g, mean $\pm$ SD	3002.3 $\pm$ 395.5
Male gender	646 (47.7)
Maternal smoking during pregnancy	111 (8.2)
Household smoking during the first year of life	395 (29.2)
Breastfeeding duration, mo	
<6	156 (11.5)
≥ 6	1198 (88.5)

SD = standard deviation.

highest quartile was significantly associated with reduced odds of wheeze in the children, showing a clear inverse exposure-response relationship (Table 3). After adjustment for confounders, the adjusted OR between extreme quartiles fell just short of the significance level, although the inverse linear trend was significant: the adjusted OR was 0.70 (95% CI, 0.49–1.003; *P* for trend = .02). An inverse exposure-response relationship between maternal EPA intake during pregnancy and infantile wheeze was significant; the adjusted OR between extreme quartiles, however, was not statistically significant at 0.73 (95% CI, 0.50–1.04; *P* for trend = .02).

Table 2
Distribution of daily intake in 1354 pregnant women at baseline*

Variable	Mean $\pm$ SD
Total energy, kJ	7390.4 $\pm$ 1976.6
Total fat, g	57.5 $\pm$ 11.0
Saturated fatty acids, g	16.6 $\pm$ 4.2
Monounsaturated fatty acids, g	20.1 $\pm$ 4.6
n-3 Polyunsaturated fatty acids, g	2.3 $\pm$ 0.7
α -Linolenic acid, g	1.7 $\pm$ 0.5
Eicosapentaenoic acid, g	0.17 $\pm$ 0.11
Docosahexaenoic acid, g	0.29 $\pm$ 0.17
n-6 Polyunsaturated fatty acids, g	10.9 $\pm$ 2.4
Linoleic acid, g	10.7 $\pm$ 2.4
Arachidonic acid, g	0.13 $\pm$ 0.04
Cholesterol, mg	283.9 $\pm$ 94.9
Meat, g	63.3 $\pm$ 28.3
Fish, g	46.9 $\pm$ 25.3

SD = standard deviation.

* Nutrient and food intake were adjusted for total energy intake using the residual method.

Maternal DHA intake showed a nonsignificant inverse exposure-response association with infantile wheeze (*P* for trend = .06). No such inverse relationships were detected for infantile eczema. Maternal intake of total fat, saturated fatty acids, monounsaturated fatty acids, total n-3 PUFA, α -linolenic acid, total n-6 PUFA, linoleic acid, arachidonic acid, and cholesterol and the ratio of n-3 to n-6 PUFA consumption were not significantly related to the odds of wheeze or eczema in the children in the multivariate model.

Neither maternal intake of meat nor fish during pregnancy was associated with the odds of wheeze or eczema in the children after adjustment for confounders (Table 4).

When classifying infants according to whether their mothers participated in the baseline survey by the 17th week of gestation (*n* = 712) or after the 18th week of gestation (*n* = 642), the adjusted ORs (95% CIs; *P* for trend) for wheeze in the highest quartile were 1.14 (0.68–1.89; .96) and 0.43 (0.24–0.74; .001), respectively, for EPA; 1.22 (0.74–2.04; .76) and 0.47 (0.27–0.81; .002), respectively, for DHA; 1.11 (0.67–1.84; .96) and 0.42 (0.24–0.73; .0008), respectively, for EPA plus DHA; and 1.13 (0.69–1.87; .81) and 0.44 (0.25–0.76; .008), respectively, for fish.

In a sensitivity analysis, which excluded 404 pregnant women who had experienced substantial changes in diet in the previous month, the adjusted ORs (95% CIs; *P* for trend) for wheeze in the highest quartile were 0.62 (0.40–0.95; .01) for EPA, 0.58 (0.38–0.89; .007) for DHA, 0.54 (0.35–0.83; .003) for EPA plus DHA, and 0.59 (0.38–0.89; .02) for fish.

Discussion

The present study found significant inverse relationships between maternal intake of both EPA and EPA plus DHA during pregnancy and the risk of wheeze, but not eczema, in Japanese children aged 23–29 months. Maternal intake levels of the other fatty acids under study as well as fish and meat in pregnancy were not associated with infantile wheeze or eczema. The prevalence values of wheeze and eczema in this study are similar to values in a previous Japanese study: the corresponding figures were 22.1% and 18.6%, respectively, among 763 infants aged 16–24 months [11]. The current results are consistent with those of a Dutch study that reported no associations between maternal fish intake during pregnancy and childhood wheeze or asthma [10] but are not consistent with reports of significant inverse relationships between maternal fish intake and childhood wheeze, asthma, and/or eczema [4–9]. Agreement was noted with the results of a previous Japanese study that showed no relationships between maternal intake of fish or meat during pregnancy and infantile wheeze or eczema; our results are inconsistent, however, with those of one study showing significant inverse associations between maternal intake of α -linolenic acid and DHA during pregnancy and infantile wheeze and significant positive associations between maternal intake of n-6 PUFA and linoleic acid during pregnancy and infantile eczema [11]. Our results are at variance with those of a Finnish study in which a significant positive relationship was observed between maternal arachidonic acid intake during pregnancy and childhood asthma and a significant inverse relationship was observed between maternal saturated fatty acid intake and childhood asthma [12]. The current results are in partial agreement with those of a UK study, which reported that the concentrations of 11 individual n-3 and n-6 PUFA in maternal blood red cells in late pregnancy were not associated with childhood wheeze or eczema [20]. Another Dutch study found that a higher ratio of n-6 to n-3 PUFA concentration in maternal plasma phospholipids in late pregnancy was related to a reduced risk of childhood eczema [21]; these findings are inconsistent with our results.

Table 3

ORs and 95% CIs for wheeze and eczema in 1354 infants aged 23–29 mo by quartiles of maternal consumption of specific fats during pregnancy

Variable*	Wheeze			Eczema		
	No. of cases	Crude OR (95% CI)	Adjusted OR (95% CI) [†]	No. of cases	Crude OR (95% CI)	Adjusted OR (95% CI) [†]
Total fat						
Q1 (46.7)	95	1.00	1.00	63	1.00	1.00
Q2 (54.5)	92	0.95 (0.68–1.34)	0.96 (0.68–1.36)	54	0.83 (0.55–1.23)	0.84 (0.55–1.26)
Q3 (60.1)	95	1.00 (0.72–1.40)	1.04 (0.73–1.47)	57	0.89 (0.60–1.31)	0.92 (0.61–1.38)
Q4 (69.0)	91	0.94 (0.67–1.32)	0.90 (0.64–1.28)	55	0.85 (0.57–1.26)	0.86 (0.57–1.29)
P for trend		.77	.64		.47	.54
Saturated fatty acids						
Q1 (12.5)	92	1.00	1.00	58	1.00	1.00
Q2 (15.4)	101	1.14 (0.81–1.59)	1.16 (0.82–1.64)	54	0.92 (0.61–1.37)	0.95 (0.63–1.44)
Q3 (17.5)	92	1.00 (0.71–1.40)	1.01 (0.71–1.44)	64	1.13 (0.76–1.67)	1.18 (0.79–1.77)
Q4 (20.8)	88	0.94 (0.67–1.32)	0.93 (0.65–1.33)	53	0.90 (0.59–1.34)	0.92 (0.61–1.40)
P for trend		.57	.55		.78	.89
Monounsaturated fatty acids						
Q1 (15.5)	96	1.00	1.00	54	1.00	1.00
Q2 (18.7)	91	0.93 (0.66–1.30)	0.91 (0.64–1.29)	65	1.25 (0.84–1.86)	1.24 (0.83–1.87)
Q3 (21.0)	104	1.12 (0.81–1.56)	1.06 (0.76–1.50)	61	1.16 (0.78–1.73)	1.15 (0.76–1.74)
Q4 (24.7)	82	0.80 (0.57–1.13)	0.75 (0.53–1.07)	49	0.89 (0.58–1.35)	0.88 (0.57–1.35)
P for trend		.34	.18		.50	.48
n-3 Polyunsaturated fatty acids						
Q1 (1.6)	95	1.00	1.00	56	1.00	1.00
Q2 (2.1)	99	1.06 (0.76–1.47)	1.05 (0.75–1.49)	53	0.93 (0.62–1.41)	0.93 (0.61–1.41)
Q3 (2.4)	96	1.02 (0.73–1.42)	0.97 (0.69–1.38)	68	1.27 (0.86–1.88)	1.21 (0.81–1.81)
Q4 (2.9)	83	0.83 (0.59–1.17)	0.79 (0.55–1.12)	52	0.91 (0.60–1.38)	0.89 (0.58–1.35)
P for trend		.28	.17		.95	.81
α-Linolenic acid						
Q1 (1.2)	91	1.00	1.00	61	1.00	1.00
Q2 (1.5)	92	1.01 (0.72–1.42)	1.02 (0.72–1.44)	52	0.82 (0.55–1.23)	0.82 (0.54–1.24)
Q3 (1.8)	97	1.09 (0.78–1.53)	1.06 (0.75–1.50)	61	1.00 (0.68–1.48)	0.97 (0.65–1.45)
Q4 (2.2)	93	1.03 (0.73–1.44)	0.96 (0.68–1.36)	55	0.88 (0.59–1.31)	0.86 (0.57–1.29)
P for trend		.80	.85		.75	.64
Eicosapentaenoic acid						
Q1 (0.07)	100	1.00	1.00	54	1.00	1.00
Q2 (0.13)	109	1.13 (0.81–1.56)	1.19 (0.84–1.67)	56	1.04 (0.69–1.57)	1.03 (0.68–1.57)
Q3 (0.17)	86	0.81 (0.58–1.14)	0.79 (0.55–1.13)	55	1.02 (0.68–1.54)	1.00 (0.66–1.53)
Q4 (0.28)	78	0.71 (0.50–1.003)	0.73 (0.50–1.04)	64	1.22 (0.82–1.83)	1.21 (0.80–1.83)
P for trend		.02	.02		.30	.35
Docosahexaenoic acid						
Q1 (0.15)	98	1.00	1.00	45	1.00	1.00
Q2 (0.23)	107	1.13 (0.81–1.57)	1.14 (0.81–1.60)	64	1.52 (1.003–2.31)	1.51 (0.99–2.32)
Q3 (0.30)	86	0.84 (0.60–1.17)	0.82 (0.58–1.17)	58	1.35 (0.89–2.07)	1.35 (0.88–2.08)
Q4 (0.45)	82	0.78 (0.55–1.10)	0.77 (0.54–1.10)	62	1.46 (0.96–2.22)	1.45 (0.95–2.24)
P for trend		.06	.06		.18	.20
Eicosapentaenoic acid + docosahexaenoic acid						
Q1 (0.22)	100	1.00	1.00	48	1.00	1.00
Q2 (0.35)	103	1.04 (0.75–1.44)	1.07 (0.76–1.51)	62	1.35 (0.90–2.05)	1.35 (0.89–2.06)
Q3 (0.47)	93	0.90 (0.65–1.26)	0.87 (0.62–1.24)	55	1.17 (0.77–1.79)	1.18 (0.77–1.82)
Q4 (0.73)	77	0.70 (0.49–0.99)	0.70 (0.49–1.003)	64	1.41 (0.94–2.12)	1.42 (0.93–2.17)
P for trend		.02	.02		.18	.19
n-6 Polyunsaturated fatty acids						
Q1 (8.4)	92	1.00	1.00	56	1.00	1.00
Q2 (10.2)	84	0.88 (0.62–1.24)	0.85 (0.59–1.21)	58	1.04 (0.70–1.56)	0.99 (0.65–1.49)
Q3 (11.5)	102	1.16 (0.83–1.62)	1.11 (0.79–1.57)	60	1.09 (0.73–1.62)	1.02 (0.68–1.54)
Q4 (13.4)	95	1.04 (0.74–1.46)	0.98 (0.69–1.39)	55	0.98 (0.65–1.47)	0.95 (0.63–1.44)
P for trend		.53	.79		.95	.84
Linoleic acid						
Q1 (8.2)	92	1.00	1.00	56	1.00	1.00
Q2 (9.9)	83	0.87 (0.61–1.22)	0.84 (0.59–1.20)	58	1.04 (0.70–1.56)	0.99 (0.66–1.50)
Q3 (11.2)	102	1.16 (0.83–1.62)	1.13 (0.80–1.60)	61	1.11 (0.74–1.66)	1.04 (0.69–1.56)
Q4 (13.0)	96	1.06 (0.75–1.48)	0.99 (0.70–1.40)	54	0.95 (0.63–1.44)	0.93 (0.61–1.41)
P for trend		.46	.71		.89	.78
Arachidonic acid						
Q1 (0.09)	91	1.00	1.00	56	1.00	1.00
Q2 (0.12)	99	1.12 (0.80–1.57)	1.12 (0.79–1.59)	61	1.11 (0.74–1.65)	1.08 (0.72–1.63)
Q3 (0.14)	92	1.02 (0.72–1.43)	1.04 (0.74–1.48)	61	1.11 (0.74–1.66)	1.07 (0.71–1.60)
Q4 (0.18)	91	1.00 (0.71–1.40)	0.95 (0.66–1.34)	51	0.89 (0.59–1.35)	0.87 (0.57–1.33)
P for trend		.85	.65		.55	.47
n-3/n-6 Polyunsaturated fatty acid ratio						
Q1 (0.17)	90	1.00	1.00	50	1.00	1.00
Q2 (0.19)	104	1.22 (0.87–1.71)	1.24 (0.88–1.75)	59	1.21 (0.81–1.84)	1.21 (0.80–1.85)
Q3 (0.21)	97	1.11 (0.79–1.56)	1.08 (0.76–1.54)	57	1.17 (0.77–1.77)	1.14 (0.75–1.76)
Q4 (0.25)	82	0.88 (0.62–1.24)	0.85 (0.59–1.22)	63	1.32 (0.88–1.98)	1.28 (0.84–1.95)
P for trend		.26	.18		.24	.33

(Continued on next page)

Table 3 (Continued)

Variable ^a	Wheeze			Eczema		
	No. of cases	Crude OR (95% CI)	Adjusted OR (95% CI) [†]	No. of cases	Crude OR (95% CI)	Adjusted OR (95% CI) [†]
Cholesterol						
Q1 (181.9)	105	1.00	1.00	56	1.00	1.00
Q2 (243.2)	85	0.74 (0.53–1.04)	0.77 (0.54–1.08)	61	1.11 (0.74–1.65)	1.09 (0.72–1.64)
Q3 (306.3)	92	0.83 (0.60–1.16)	0.83 (0.59–1.17)	65	1.20 (0.81–1.78)	1.20 (0.80–1.80)
Q4 (402.3)	91	0.81 (0.58–1.14)	0.79 (0.56–1.12)	47	0.81 (0.53–1.23)	0.79 (0.52–1.22)
P for trend		.38	.29		.34	.31

^a Quartile medians in grams per day (except for cholesterol, milligrams per day) adjusted energy intake using the residual method are given in parentheses, except for the ratio of n-3 to n-6 polyunsaturated fatty acids, which was based on crude intake in grams per day.

[†] Adjustment for maternal age, gestation at baseline, region of residence at baseline, number of children at baseline, maternal and paternal education, family income, maternal and paternal history of asthma, atopic eczema, and allergic rhinitis, baby's birth weight, baby's sex, maternal smoking during pregnancy, household smoking during the first year of life, and breastfeeding duration.

PUFA can influence the Th1 and Th2 balance [2]. Interleukin (IL)-13 is a critical mediator in the pathogenesis of allergic inflammation [22]. In a randomized double-blind, placebo-controlled trial among 83 atopic pregnant Australian women, cord plasma IL-13 levels were significantly lower in neonates whose mothers received fish oil supplements (3.7 g n-3 PUFA/d) from 20 weeks gestation until delivery compared with the placebo group [23]. A European multicenter intervention study demonstrated that fish oil supplementation consisting of 0.5 g DHA and 0.15 g EPA from the 22nd week of gestation until delivery was associated with decreased messenger RNA (mRNA) levels of Th2-related IL-4, IL-13, and CC chemokine receptor 4 (CCR4) in cord blood, decreased frequencies of cord blood natural killer cells and CCR3⁺CD8⁺ T cells, increased Th1-related transforming growth factor beta mRNA not only in maternal peripheral blood at delivery but also in cord blood, and increased mRNA levels of Th1-related IL-1 and interferon gamma in maternal blood only [24]. A recent systematic review found that maternal n-3 PUFA supplementation during pregnancy significantly reduced the risk of childhood asthma but had no effect on childhood eczema [25]. Higher maternal marine-origin n-3 PUFA intake during pregnancy might reduce the risk of wheeze and asthma in children, although any similar beneficial effect on childhood eczema is probably negligible.

Linoleic acid is a precursor of arachidonic acid, which is a substrate for eicosanoid synthesis. According to a review by Moore and Peebles [26], prostaglandin D₂, prostaglandin F_{2α}, and thromboxane A₂ increase allergic inflammation, whereas prostaglandin E₂ and prostaglandin I₂ inhibit allergen-induced inflammatory responses. In a U.S. birth cohort study, higher levels of cord blood EPA and arachidonic acid were each related to reduced lymphocyte proliferation and interferon gamma levels in response to allergen

stimulation, whereas higher levels of linoleic acid were related to higher allergen-stimulated IL-13 levels [27]. With respect to the above-mentioned arachidonic acid–associated attenuation of immune responses as well as the possible positive association between arachidonic acid intake and production of prostaglandin E₂ and prostaglandin I₂, if the beneficial effect of antenatal n-6 PUFA exposure on childhood allergic manifestation counteracts the negative effect, the present results suggesting null associations between maternal intake of n-6 PUFA, linoleic acid, and arachidonic acid during pregnancy and infantile wheeze or eczema are reasonable.

Long chain n-3 PUFAs inhibit arachidonic acid incorporation into cell membranes and inhibit arachidonic acid metabolism to eicosanoids [28]. Given that higher intake of EPA and EPA plus DHA inhibits the production of prostaglandin D₂, prostaglandin F_{2α}, and thromboxane A₂, the observed inverse associations might be reasonable although null relationships were found between such intake and eczema.

Several methodological limitations of this study warrant mention. The definitions of wheeze and eczema were based on questions from the International Study of Asthma and Allergies in Childhood although validation tests of these questions have not been performed for Japanese infants. No attempt was made to ascertain outcome status through reviews of medical records. Data on IgE levels were not available in this study. Furthermore, wheeze in infancy is known not to be a good predictor of asthma over the longer term [29]. The exposures under study were not likely to influence the identification of infantile wheeze and eczema; thus, the possibility of nondifferential outcome misclassification might have biased the magnitude of the observed associations toward the null.

Table 4

ORs and 95% CIs for wheeze and eczema in 1354 infants aged 23–29 mo by quartiles of maternal consumption of meat and fish during pregnancy

Variable ^a	Wheeze			Eczema		
	No. of cases	Crude OR (95% CI)	Adjusted OR (95% CI) [†]	No. of cases	Crude OR (95% CI)	Adjusted OR (95% CI) [†]
Meat						
Q1 (34.1)	86	1.00	1.00	47	1.00	1.00
Q2 (52.6)	102	1.26 (0.90–1.77)	1.31 (0.92–1.86)	69	1.58 (1.06–2.39)	1.60 (1.06–2.43)
Q3 (69.0)	82	0.94 (0.66–1.33)	0.92 (0.64–1.32)	56	1.23 (0.81–1.88)	1.21 (0.79–1.87)
Q4 (93.6)	103	1.28 (0.91–1.79)	1.27 (0.90–1.80)	57	1.25 (0.82–1.91)	1.26 (0.82–1.93)
P for trend		.34	.43		.61	.61
Fish						
Q1 (23.4)	95	1.00	1.00	55	1.00	1.00
Q2 (37.5)	96	1.01 (0.72–1.41)	1.01 (0.72–1.43)	43	0.75 (0.48–1.15)	0.72 (0.46–1.12)
Q3 (49.8)	104	1.14 (0.82–1.58)	1.13 (0.80–1.59)	63	1.18 (0.79–1.76)	1.18 (0.78–1.77)
Q4 (71.3)	78	0.76 (0.54–1.08)	0.74 (0.51–1.06)	68	1.29 (0.87–1.92)	1.29 (0.86–1.93)
P for trend		.15	.11		.06	.06

^a Quartile medians in grams per day adjusted energy intake using the residual method are given in parentheses.

[†] Adjustment for maternal age, gestation at baseline, region of residence at baseline, number of children at baseline, maternal and paternal education, family income, maternal and paternal history of asthma, atopic eczema, and allergic rhinitis, baby's birth weight, baby's sex, maternal smoking during pregnancy, household smoking during the first year of life, and breastfeeding duration.

Our DHQ could only approximate consumption and was designed to assess dietary intake for 1 month before completing the questionnaire. Any nondifferential exposure misclassification would have led to an underestimation of values in our results. Dietary assessment was carried out anywhere from the fifth to the 39th week of pregnancy; however, gestation at baseline was controlled for. When our subjects were divided into two groups according to gestation at baseline, significant inverse associations were observed between maternal intake of EPA, DHA, and EPA plus DHA during pregnancy and wheeze in infants whose mothers participated in the baseline survey after the 18th week of gestation ($n = 642$) but not in infants whose mothers participated in the baseline survey before or during the 17th week of gestation ($n = 712$). Our DHQ may provide better information on dietary habits over the preceding month than biochemical status samples do, whereas intake data based on our DHQ may be socially confounded and also may not account for individual metabolic variations which may affect serum fatty acid levels or transfer to the child. Information on dietary supplements that included EPA and/or DHA was not available, but it might not be necessary to take such supplements into consideration among our study subjects because pregnant Japanese women are generally not advised to take such supplements. Only a small number of our participants used vitamin C (4.4%), multivitamin (6.0%), and calcium (6.0%) supplements at least once a week, although 26.6% used vitamin B complex at least once a week. Nevertheless, supplementation is unlikely to be random with respect to factors such as social class, which may confound the results. Substantial changes in diet in the previous month were experienced by 404 pregnant women because of nausea gravidarum (383 women), maternal and fetal health reasons (19 women), or other reasons (2 women). After these 404 women were excluded, higher maternal intake levels of not only EPA and EPA plus DHA but also DHA and fish during pregnancy were significantly related to a reduced risk of childhood wheeze.

Of the 1757 participants at baseline, 395 mother-child pairs did not participate in the fifth survey. There were no material differences between the 395 nonparticipants and the 1362 participants in the fifth survey with regard to distribution of number of children, maternal and paternal history of asthma, atopic eczema, allergic rhinitis, and maternal intake of dietary factors under study excluding meat. Compared with nonparticipants in the fifth survey, participants were more likely to be older, to have participated in the baseline survey earlier in their gestation, to live in Fukuoka Prefecture, to report high maternal and paternal educational levels and high household income, and to have a low meat intake. Moreover, at baseline, we could not estimate the participation rate because we do not have exact figures for the number of pregnant women who were provided with a set of leaflets explaining the KOMCHS, an application form, and a self-addressed and stamped return envelope by the 423 collaborating obstetric hospitals. Our subjects were probably not representative of Japanese women in the general population. For example, a population census conducted in 2000 in Fukuoka Prefecture found that the percentages of women aged 30–34 years with younger than 13 years, 13–14 years, 15 years or older, and an unknown number of years of education were 52.0%, 31.5%, 11.8%, and 4.8%, respectively [30]. The corresponding figures for this study were 21.6%, 33.6%, 44.8%, and 0.0%, respectively. Thus, our study subjects were more educated and probably more aware of health topics than women in the general population.

Although adjustment was made for several confounding factors, residual confounding effects could not be ruled out. Variation in the children's dietary habits may confound the present results. The observed null associations between maternal intake of DHA or fish during pregnancy and infantile wheeze might be ascribed to insufficient statistical power.

In conclusion, the results of this prebirth cohort study in Japan suggest that higher maternal intake of EPA and EPA plus DHA during pregnancy may reduce the risk of infantile wheeze. Because no such inverse associations were observed between EPA or EPA plus DHA intake and infantile eczema, we cannot rule out the possibility that such intake might be protective against respiratory infections rather than atopy. Further prospective studies and trials are required to draw conclusions as to the question of whether maternal fatty acid intake during pregnancy is related to the risk of childhood allergic disorders.

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