Table 4. Odds Ratios (ORs) and 95% Confidence Intervals (CIs) for Allergic Rhinitis by Quartiles of Specific Types of Dietary Fat, OMCHS, Japan

Variable[1]	Prevalence	Crude OR (95% CI)	Adjusted OR (95% CI)[2]
Total fat			
Q1 (44.0)	39/250 (15.6%)	1.00	1.00
Q2 (51.4)	34/251 (13.6%)	0.85 (0.51–1.39)	0.95 (0.56–1.62)
Q3 (56.8)	29/250 (11.6%)	0.71 (0.42–1.19)	0.71 (0.41–1.23)
Q4 (64.4)	39/251 (15.5%)	1.00 (0.61–1.62)	1.02 (0.61–1.72)
p for trend		0.83	0.82
Saturated fatty acids			
Q1 (13.0)	40/250 (16.0%)	1.00	1.00
Q2 (15.5)	34/251 (13.6%)	0.82 (0.50–1.35)	0.82 (0.48–1.38)
Q3 (17.3)	39/250 (15.6%)	0.97 (0.60–1.57)	1.00 (0.60–1.68)
Q4 (20.6)	28/251 (11.2%)	0.66 (0.39–1.10)	0.64 (0.37–1.11)
p for trend		0.20	0.21
Monounsaturated fatty acids			
Q1 (14.9)	38/250 (15.2%)	1.00	1.00
Q2 (17.9)	33/251 (13.2%)	0.85 (0.51–1.40)	0.88 (0.51–1.51)
Q3 (19.8)	28/250 (11.2%)	0.70 (0.41–1.18)	0.65 (0.37–1.12)
Q4 (23.1)	42/251 (16.7%)	1.12 (0.70–1.81)	1.15 (0.69–1.92)
p for trend		0.78	0.85
n-3 Polyunsaturated fatty acids			
Q1 (1.6)	39/250 (15.6%)	1.00	1.00
Q2 (2.1)	37/251 (14.7%)	0.94 (0.57–1.53)	0.94 (0.56–1.58)
Q3 (2.4)	28/250 (11.2%)	0.68 (0.40–1.14)	0.80 (0.46–1.38)
Q4 (3.0)	37/251 (14.7%)	0.94 (0.57–1.53)	0.94 (0.56–1.57)
p for trend		0.53	0.69
Eicosapentaenoic and docosahexaenoic acids			
Q1 (0.24)	47/250 (18.8%)	1.00	1.00
Q2 (0.41)	35/251 (13.9%)	0.70 (0.43–1.13)	0.63 (0.38–1.05)
Q3 (0.55)	32/250 (12.8%)	0.63 (0.39–1.03)	0.56 (0.33–0.94)
Q4 (0.83)	27/251 (10.8%)	0.52 (0.31–0.86)	0.56 (0.32–0.96)
p for trend		0.01	0.03
Eicosapentaenoic acid			
Q1 (0.08)	45/250 (18.0%)	1.00	1.00
Q2 (0.15)	36/251 (14.3%)	0.76 (0.47–1.23)	0.72 (0.43–1.19)
Q3 (0.21)	33/250 (13.2%)	0.69 (0.42–1.13)	0.62 (0.37–1.04)
Q4 (0.33)	27/251 (10.8%)	0.55 (0.33–0.91)	0.60 (0.35–1.03)
p for trend		0.02	0.05
Docosahexaenoic acid			
Q1 (0.16)	46/250 (18.4%)	1.00	1.00
Q2 (0.26)	36/251 (14.3%)	0.74 (0.46–1.19)	0.65 (0.38–1.08)
Q3 (0.34)	31/250 (12.4%)	0.63 (0.38–1.02)	0.56 (0.33–0.94)
Q4 (0.50)	28/251 (11.2%)	0.56 (0.33–0.92)	0.59 (0.34–1.00)
p for trend		0.02	0.04
n-6 Polyunsaturated fatty acids			
Q1 (8.3)	38/250 (15.2%)	1.00	1.00
Q2 (10.1)	31/251 (12.4%)	0.79 (0.47–1.31)	0.86 (0.50–1.46)
Q3 (11.5)	24/250 (9.6%)	0.59 (0.34–1.02)	0.59 (0.33–1.04)
Q4 (13.5)	48/251 (19.1%)	1.32 (0.83–2.11)	1.30 (0.79–2.15)
p for trend		0.36	0.47
n-3/n-6 Polyunsaturated fatty acid ratio			
Q1 (0.17)	40/250 (16.0%)	1.00	1.00
Q2 (0.19)	33/251 (13.2%)	0.80 (0.48–1.31)	0.85 (0.50–1.43)
Q3 (0.22)	40/250 (16.0%)	1.00 (0.62–1.62)	1.03 (0.62–1.72)
Q4 (0.25)	28/251 (11.2%)	0.66 (0.39–1.10)	0.78 (0.45–1.35)
p for trend		0.23	0.55
Cholesterol			
Q1 (158.1)	35/250 (14.0%)	1.00	1.00
Q2 (223.2)	38/251 (15.1%)	1.10 (0.67–1.81)	1.07 (0.63–1.82)
Q3 (291.8)	37/250 (14.8%)	1.07 (0.65–1.76)	1.13 (0.66–1.92)
Q4 (383.8)	31/251 (12.4%)	0.87 (0.51–1.45)	0.83 (0.48–1.45)
p for trend		0.59	0.59

[1] Quartile medians in g/day (except for cholesterol; mg/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 were based on crude intake in g/day.

[2] Adjustment for age, gestation, parity, cigarette smoking, passive smoking at home and at work, indoor domestic pets, family history of asthma, atopic eczema, and allergic rhinitis, family income, education, mite antigen level in house dust, changes in diet in the previous 1 month, season when data were collected, and body mass index (continuous).

total fat, saturated fatty, monounsaturated fatty, and n-3 polyunsaturated fatty acids, and cholesterol and the ratio of n-3 to n-6 polyunsaturated fatty acids were not independently associated with the prevalence of allergic rhinitis.

DISCUSSION

The present study found that intake of eicosapentaenoic and docosahexaenoic acids was independently associated with a decreased prevalence of allergic rhinitis. The current study failed to verify a clear inverse association between fish intake and the prevalence of allergic rhinitis although the linear trend was of statistically borderline significance. Intake of n-6 polyunsaturated fatty acids in the third quartile but not the second and fourth quartiles showed a tendency for an inverse association with the prevalence of allergic rhinitis. There was no measurable relationship of consumption of meat, eggs, dairy products, total fat, saturated, monounsaturated, and n-3 polyunsaturated fatty acids, and cholesterol or the ratio of n-3 to n-6 polyunsaturated fatty acids with allergic rhinitis. A previous cross-sectional study in Japanese women found that intake of n-6 polyunsaturated fatty acids was positively associated with seasonal allergic rhinoconjunctivitis in spring whereas there were no statistically significant relationships between consumption of saturated, monounsaturated, and n-3 polyunsaturated fatty acids and symptoms of allergic rhinoconjunctivitis [18]. In a case-control study in German adults, intake of oleic acid was positively associated with hay fever whereas intake of eicosapentaenoic acid was inversely related to hay fever although there was no evident association with saturated or n-6 polyunsaturated fatty acids [17]. A cross-sectional study among German adults demonstrated that a high red cell membrane level of eicosapentaenoic acid was inversely associated with allergic rhinitis whereas there was an inverse relationship between α-linolenic acid intake and allergic rhinitis [26]. No association was found between fish intake and allergic rhinitis in a cross-sectional study in Italian children and a case-control study in Finnish children [12, 13]. The present results are partially consistent with these findings.

The differences between Japanese and Western diets should be taken into consideration when interpreting our results. In particular, intake of eicosapentaenoic and docosahexaenoic acids in Japan was much higher than in Western countries. In 20 Canadian pregnant women, mean intake of α-linolenic, eicosapentaenoic and docosahexaenoic acids was estimated to be 1295, 35, and 82 mg/day, respectively, which was determined by direct quantitation of duplicate food collections [27]. The corresponding figures in 85 middle-aged Japanese women were 1589, 314, and 571 mg/day, respectively, which were obtained from 7-day weighed diet records [28]. The values of both eicosapentaenoic and docosahexaenoic acids among Canadian pregnant women were about half of the median values of the first quartile of eicosapentaenoic and docosahexaenoic acid intake in our population. Among middle-aged Japanese women, values were nearly the same as the median values of the fourth quartile intake of these nutrients in our subjects.

Our findings of an inverse association between intake of eicosapentaenoic and docosahexaenoic acids and the prevalence of allergic rhinitis may be ascribed to anti-inflammatory effects of marine-derived n-3 polyunsaturated fatty acids. Arachidonic acid-derived inflammatory mediators, prostaglandin E_2 and leukotriene B_4, are factors that control the severity of allergic inflammation [29]. Prostaglandin E_2 influences the Th1 to Th2 ratios and subsequently inhibits interferon-γ production, with no effect on IL-4, thus stimulating IgE synthesis [29]. Eicosapentaenoic acid can inhibit arachidonic acid metabolism competitively via enzymatic pathways and, thus, can suppress production of n-6 eicosanoid inflammatory mediators [30]. n-3 Fatty acids may also affect immune cell function by modulating cytokine, Ig and adhesion molecule production [29]. The present findings are partially compatible with this hypothesis although data on these molecules were not available in the present study. A clinical trial demonstrated that the proportions of eicosapentaenoic and docosahexaenoic acids in plasma phospholipids and neutrophil lipids increased significantly after supplementation with eicosapentaenoic or docosahexaenoic acid and that docosahexaenoic acid supplementation decreased T lymphocyte activation [31]. We could not use a direct marker of fat intake such as plasma and erythrocyte concentrations of fatty acids in this study, however. On the other hand, previous studies among healthy humans reported that fish oil supplementation (2.4 g/day) suppressed the production of IL-2 [32, 33]. Two intervention studies demonstrated that there were no effects of supplementation with γ-linolenic, eicosapentaenoic, and docosahexaenoic acids on the production of IL-2 and interferon-γ [34,35].

In the current study, intake of fish was not statistically significantly related to a decreased prevalence of allergic rhinitis. Unrecognized active agents in fish might have counteracted the advantage of intake of fish against allergic rhinitis. For example, methylmercury and dioxins are accumulated in fish and shellfish through the marine food web. Lack of association between intake of n-3 polyunsaturated fatty acids and allergic rhinitis in this study could be attributed to our finding that there was no relationship between α-linolenic acid intake and allergic rhinitis (data not shown). We also cannot confirm the hypothesis that a balance between n-3 and n-6 polyunsaturated fatty acid metabolism is important in the manifestation of allergic disorders. In a case-control study of German adults, a significant inverse dose-response association between the ratio of n-6 to n-3 polyunsaturated fatty acids and the risk of hay fever was reported [17]. On the other hand, a cross-sectional study showed that a high n-6 to n-3 ratio was significantly positively related to hay fever in males and that the ratio was not statistically significantly associated with hay fever in females [16]. In the typical Western diet, 20- to 25-fold more n-6 fats than n-3 fats are consumed [30]. The median values of the ratio of n-3 to n-6

polyunsaturated fatty acids were 0.145, 0.145, and 0.206 in control subjects in the case-control German study [17], females in the cross-sectional German study [16], and the present study, respectively. A clear inverse association between the ratio of n-3 to n-6 fatty acids and allergic rhinitis may be substantiated when consumption of n-3 polyunsaturated fatty acids is very low.

The present study had several methodological strengths. Study subjects were homogeneous in terms of all being pregnant and having the same residential background. Extensive data on potential confounding factors were controlled for. However, we did not incorporate external factors such as aeroallergens and air pollution. Intake of dietary variables under investigation was estimated using a self-administered semiquantitative dietary assessment questionnaire. Since we did not assess the real dietary habits of the subjects, the chance of misclassification might be inevitable. According to validation tests, the correlation coefficients for nutrient intake between those estimated from the diet history questionnaire and those observed by 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 women [20]. A highly positive correlation was also observed between marine-origin n-3 polyunsaturated fatty acid intake estimated by the diet history questionnaire and the corresponding concentration in the serum phospholipid fraction ($r = 0.51$ and 0.69 in men and women, respectively) [21]. Allergic rhinitis sufferers might not be aware of the ill effects of diet. Such an assumption would lead to bias toward the null. Our diet history questionnaire was designed to assess recent dietary intake, i.e. for 1 month prior to completing the questionnaire. This disadvantage is likely to be alleviated after adjustment for the season when data were collected, however. Changes in diet in the past 1 month were controlled for because pregnant females are likely to change their diet for reasons such as nausea gravidarum. Information on intake of *trans* fatty acids was not available in this study although an ecological study in European adolescents found a positive association between *trans* fatty acids and the prevalence of allergic rhinoconjunctivitis [36].

Other weaknesses also should be borne in mind. In Neyagawa City, the participation rate was low (17.2%). We were not able to evaluate a difference between participants and non-participants in Neyagawa City, because data on personal characteristics among the non-participants were not available. Regarding the remaining 375 participants, who were not residents of Neyagawa City, we were not able to calculate the participation rate because the exact number of eligible subjects was not available. Also, we could not compare participants with non-participants in the 4 collaborating hospitals and 6 municipalities. Our subjects were an unrepresentative sample of Japanese females in the general population, and the present findings may not be generalized. In fact, educational levels were higher in the present study population than in the general population. According to the 2000 population census of Japan, the proportions of females aged 30 to 34 years in Osaka Prefecture with years of education of < 13, 13–14, 15+, and unknown were 49.2, 32.3, 13.6, and 4.9%, respectively [37]. The corresponding figures for the current study were 32.2, 41.2, 26.6, and 0.0%, respectively. Japanese cedar pollinosis is a seasonal disorder with a high prevalence and is often undiagnosed [1]. We did not use validated diagnostic criteria such as those reported in the International Study of Asthma and Allergies in Childhood. Because the definition of allergic rhinitis was based on drug treatment, there was a loss of milder sufferers. Moreover, females who want to become pregnant or who are pregnant might tend to avoid drugs. The consequence would have been an underestimation of values in our results. The lack of a significant inverse association between fish intake and allergic rhinitis might be attributed to an insufficient statistical power. If the analysis had been able to include the total study population of 1600 pregnant women, the inverse association would have reached the level of significance.

A relationship between pregnancy and a shift to the Th2 side of the immune response has been indicated [38] whereas the importance of the role of NK and IL-12, IL-15, and IL-18 tripods in successful or failed pregnancy in humans was suggested beyond the Th1/Th2 paradigm [39]. Rhinitis symptoms during pregnancy may be attributed to the hormonal changes in pregnancy. However, rhinitis solely ascribed to pregnancy may not be a distinct entity because most pregnant women do not have significant nasal symptoms [38]. In the present study, 105 of 141 current allergic rhinitis sufferers (74.5%) had been treated with medications at some time for 1 or more years.

In conclusion, our findings suggest that intake of eicosapentaenoic and docosahexaenoic acids may be associated with a reduced prevalence of allergic rhinitis although we have not found any evidence to indicate that n-6 fatty acids are related to an increased prevalence of allergic rhinitis. There was a tendency for an inverse association between fish intake and allergic rhinitis. The present results regarding intake of eicosapentaenoic and docosahexaenoic acids may support existing recommendations for intake of these nutrients in adults such as a minimum combined intake of 500 mg/day eicosapentaenoic and docosahexaenoic acids for cardiovascular health based on the International Society for the Study of Fatty Acids and Lipids 2004 although the outcome under study is allergic rhinitis. Because this was a cross-sectional study, we could not establish a cause and effect relationship for the associations under study. Further evaluation in prospective studies may clarify the relation between dietary intake of fatty acids and foods high in fatty acids and allergic rhinitis.

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APPENDIX

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Home environment and suspected atopic eczema in Japanese infants: The Osaka Maternal and Child Health Study

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Atopic eczema is most commonly diagnosed in children under the age of 5 yr. Environmental factors during pregnancy or in early life may confer risk for childhood atopic eczema. The present prospective study examined the relationship of the perinatal home environment and the risk of suspected atopic eczema among Japanese infants under the age of 1. Study subjects were 865 parent–child pairs. The term 'suspected atopic eczema' was used to define an outcome based on our questionnaire at 2–9 months postpartum. Adjustment was made for maternal age, gestation, family income, maternal and paternal education, maternal and paternal history of asthma, atopic eczema, and allergic rhinitis, time of delivery before the second survey, baby's older siblings, baby's sex, and baby's birth weight. A high mite allergen level from maternal bedclothes and mold in the kitchen during pregnancy were significantly associated with an increased risk of suspected atopic eczema. Frequent vacuuming practices during pregnancy and giving the infant a bath or shower at least once a day were significantly inversely related to the risk of suspected atopic eczema. Maternal smoking, maternal use of a synthetic duvet and pillow, carpet use in the living room and maternal bedroom, indoor domestic pets, no ducted heating appliance, and gas use for cooking during pregnancy and household smoking in the same room as the infant, infant's synthetic duvet, carpet use in the infant's room, or vacuuming the infant's room were not related to the risk of suspected atopic eczema. High house dust mite allergen levels and mold in the kitchen during pregnancy may increase the risk of infantile atopic eczema, whereas frequent vacuuming practices during pregnancy and giving the infant a bath or shower at least once a day may protect against infantile atopic eczema.

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Atopic eczema is the most common chronic inflammatory skin disease in children in Japan as well as in Western countries (1, 2). An epidemiologic study of Japanese schoolchildren showed that the lifetime prevalence of atopic eczema rose from 15.0% in 1985 to 24.1% in 1993 (3). Because genetic stock is not likely to have changed over the past decades, environmental factors appear to play an important role in the manifestation of atopic eczema.

An environmental factor in relation to westernization is the home environment, which might explain the increase in atopic eczema. For example, increased indoor dampness because of

improved insulation is likely to be linked to high exposure to house dust mite allergen which could induce and maintain atopic eczema either by means of penetration of house dust mite allergen through damaged stratum corneum or by crossing the respiratory barrier (4). It remains controversial whether indoor use of gas, indoor domestic pets, mold, and environmental tobacco smoke are associated with the risk of atopic eczema (5–8).

Atopic eczema is most commonly diagnosed in children under the age of 5 yr. Environmental factors during pregnancy or in early life may confer risk for childhood atopic eczema. The aim of the present study was to examine the relationship of the perinatal home environment and the risk of suspected atopic eczema among Japanese infants under the age of 1 using data from a prospective cohort study: the Osaka Maternal and Child Health Study (OMCHS).

Methods

Study population

The OMCHS is an ongoing prospective cohort study that investigates preventive and risk factors for maternal and child health problems such as allergic disorders. The OMCHS requested that pregnant females complete a baseline survey, which was followed by several postnatal surveys. In Japan, when females become pregnant, they notify the municipality of the domicile of the conception and the municipality provides them with a maternal and child health handbook. Eligible subjects were those women who became pregnant in Neyagawa City, which is one of the 43 municipalities in Osaka Prefecture, a metropolis in Japan with a total population of approximately 8.8 million. During the period from November 2001 to March 2003, the Neyagawa City Government provided all pregnant females with a set of leaflets explaining the OMCHS, an application form, and a self-addressed and stamped return envelop together with the maternal and child health handbook. Research technicians asked all of the eligible females to take part in the OMCHS by telephone, excluding pregnant females who had already returned the application form to the data management center. Of the 3639 eligible subjects in Neyagawa City, 627 pregnant females (17.2%) participated in the OMCHS. Eight pregnant females who did not live in Neyagawa City but who had become aware of the OMCHS at an obstetric clinic before August 2002 decided by themselves to participate in the OMCHS. Moreover, there were 77 participants who received explanations of the OMCHS from public health nurses in six other municipalities from August 2002 to March 2003. From October 2002 to March 2003, 290 participants were recruited from a university hospital and three obstetric hospitals in three other municipalities; these women were recommended for participation in the OMCHS by an obstetrician. Finally, a total of 1002 pregnant women gave their fully informed consent in writing and completed the baseline survey. Of the 1002 females, 867 mothers participated in the second survey at 2–9 months postpartum. Missing data on the baby's birth weight caused the exclusion of two mother–child pairs. There were 865 mother–child pairs left for analysis. The ethics committee of the Osaka City University School of Medicine approved the OMCHS.

Measurements

At baseline, each participant filled out a set of two self-administered questionnaires and collected a dust sample from a 1 m^2 area of the bedclothes for 1 min using a vacuum cleaner fitted with a collection apparatus. Moreover, a self-administered questionnaire was used in the second survey. Participants mailed these materials to the data management center. Research technicians completed missing or illogical data by telephonic interview.

In the baseline survey, a questionnaire inquired about maternal age, gestation, smoking habits, family income, maternal and paternal education, maternal and paternal history of asthma, atopic eczema, and allergic rhinitis, types of duvet and pillow used, carpet use, vacuuming practices, indoor domestic pets, presence of mold in the kitchen, current heating system, and the types of appliances used for cooking. A paternal or maternal history of asthma, atopic eczema, and allergic rhinitis was defined as positive if the respective parent had been treated with medications for any of these allergic disorders at some time prior to the start of the survey. Another instrument was a validated self-administered diet history questionnaire. Data regarding diet were not used in the current study.

Antigen levels from extracts of fine dust fractions were measured by a double-antibody sandwich enzyme-linked immunosorbent assay using a soluble antigen prepared from whole *Dermatophagoides farinae* mite bodies as a reference standard and were expressed as antigen equivalent in $\mu g/m^2$ of surface area (Mitey

checker®, Shinto Fine Co., Ltd, Osaka, Japan; 9, 10). Antigen levels were semiquantitatively classified with scores of − (< 2 $\mu g/m^2$), ± (5 $\mu g/m^2$), + (10–15 $\mu g/m^2$), and + + (> 35 $\mu g/m^2$).

A self-administered questionnaire in the second survey elicited information on baby's sex, birth weight, date of birth of the infant born after the baseline survey, number of baby's older siblings, smoking in the household, types of infantile duvet used, carpet use in the infant's room, vacuuming practices in the infant's room, frequency of bathing or showering the infant, and atopic eczema status. Suspected atopic eczema was considered to be present if the mother selected any one of the following answers to the written question 'Has your child been diagnosed by a physician as having atopic eczema and treated with topical steroids?': (i) my child has been diagnosed with atopic eczema and treated with topical steroids (n = 28); (ii) my child has been diagnosed with atopic eczema but has not been treated with topical steroids (n = 13); (iii) my child has been diagnosed with atopic eczema and treated with a unknown ointment (n = 1); (iv) my child has been diagnosed as possibly having atopic eczema and has been treated with topical steroids (n = 33); or (v) my child has been diagnosed as possibly having atopic eczema but has not been treated with topical steroids (n = 1). Of the 865 infants, 76 (8.8%) were estimated to have had suspected atopic eczema since birth until the time of the second survey.

Statistical analysis

Logistic regression analysis was used to estimate crude odds ratio (ORs) and 95% confidence intervals (CIs) of suspected atopic eczema associated with the exposures under study. Multiple logistic regression analysis was used to control for confounding factors. Covariates included in the multivariate models were maternal age, gestation, family income, maternal and paternal education, maternal and paternal history of asthma, atopic eczema, and allergic rhinitis, time of delivery before the second survey, baby's older siblings, baby's sex, and baby's birth weight. Vacuuming practices were classified into two categories (less than three times and three times or more per week); bathing or showering the infant into two (less than and at least once a day); maternal age into three (< 29, 29–31, and 32+ yr); gestation into three (< 15, 15–20, and 21+ wk); family income into three (< 4,000,000, 4,000,000–5,999,999, and 6,000,000+ yen/yr); maternal and paternal education into three (< 13, 13–14, and 15+ yr); time of delivery before the second survey into two (< 4 and 4+ months); number of baby's older siblings into two (0 and 1+); and baby's birth weight into two (< 2500 and 2500+ g). All computations were performed using SAS software, version 9.1 (SAS Institute, Inc., Cary, NC, USA).

Results

Table 1 shows the distribution of selected factors among 865 parent–child pairs who completed the second survey. About 30% of mothers were from 29 to 31 yr of age at baseline. About 70% of the mothers took part in the baseline survey by the 20th week of gestation. The second survey was carried out at 2–9 months postpartum, with 432, 339, and 63 parent–child pairs participating at 3, 4, and 5 months after delivery, respectively. The remaining 31 pairs completed the survey at 2, 6,

Table 1. Distribution of selected characteristics of 865 parent–child pairs, OMCHS, Japan

Variable	N (%)
Baseline characteristics	
Maternal age (yr)	
<29	324 (37.5)
29–31	253 (29.3)
32+	288 (33.3)
Gestation (wk)	
<15	317 (36.7)
15–20	274 (31.7)
21+	274 (31.7)
Family income (yen/yr)	
<4,000,000	250 (28.9)
4,000,000–5,999,999	345 (39.9)
6,000,000+	270 (31.2)
Maternal education (yr)	
<13	257 (29.7)
13–14	367 (42.4)
15+	241 (27.9)
Paternal education (yr)	
<13	333 (38.5)
13–14	144 (16.7)
15+	388 (44.9)
Maternal history of asthma	89 (10.3)
Maternal history of atopic eczema	133 (15.4)
Maternal history of allergic rhinitis	291 (33.6)
Paternal history of asthma	74 (8.6)
Paternal history of atopic eczema	81 (9.4)
Paternal history of allergic rhinitis	169 (19.5)
Characteristics at the postnatal assessment	
Time of delivery before the assessment (months)	
<4	436 (50.4)
4+	429 (49.6)
Baby's older siblings: 1 or more	440 (50.9)
Baby's sex (male)	452 (52.3)
Baby's birth weight (g)	
<2500	54 (6.2)
2500+	811 (93.8)

7, 8, or 9 months postpartum. About 6% of infants had a birth weight < 2500 g.

Crude and adjusted ORs and their 95% CIs for suspected atopic eczema in relation to the home environment during pregnancy are provided in Table 2. High mite allergen level in excess of 35 $\mu g/m^2$ from maternal bedclothes during pregnancy was significantly associated with an increased risk of suspected atopic eczema. The positive association was slightly strengthened after adjustment for maternal age, gestation, family income, maternal and paternal education, maternal and paternal history of asthma, atopic eczema, and allergic rhinitis, time of delivery before the second survey, baby's older siblings, baby's sex, and baby's birth weight (adjusted OR: 3.68; 95% CI: 1.68–7.79). Frequent vacuuming practices were independently inversely related to the risk of suspected atopic eczema: the multivariate OR for comparison of three times or more with less than three times per week of vacuuming the living room was 0.50 (95% CI: 0.29–0.84) and for vacuuming the maternal bedroom it was 0.53 (95% CI: 0.31–0.89). Mold in the kitchen was independently associated with a 1.9-fold increased risk of suspected atopic eczema after multivariate adjustment. Maternal smoking, maternal synthetic duvet and pillow, carpet use in the living room and maternal bedroom, indoor domestic pets, no ducted heating appliance, and gas use for cooking were not statistically significantly related to the risk of suspected atopic eczema.

Table 2. Crude and adjusted odds ratios and 95% confidence intervals for suspected atopic eczema in relation to the home environment during pregnancy in 865 infants, OMCHS, Japan

Home environmental factor	Risk (%)	Crude odds ratio (95% CI)	Adjusted odds ratio (95% CI)*
Maternal smoking			
No	68/752 (9.0)	1.00	1.00
Yes	8/113 (7.1)	0.77 (0.33–1.55)	0.70 (0.29–1.47)
Maternal synthetic duvet			
No	56/684 (8.2)	1.00	1.00
Yes	20/181 (11.1)	1.39 (0.80–2.35)	1.40 (0.79–2.41)
Maternal synthetic pillow			
No	38/447 (8.5)	1.00	1.00
Yes	38/418 (9.1)	1.08 (0.67–1.73)	1.20 (0.74–1.95)
Mite allergen level from maternal bedclothes†			
–	28/377 (7.4)	1.00	1.00
±	20/259 (7.7)	1.04 (0.57–1.89)	1.17 (0.63–2.16)
+	15/169 (8.9)	1.21 (0.62–2.31)	1.28 (0.64–2.47)
++	13/60 (21.7)	3.45 (1.63–7.01)	3.68 (1.68–7.79)
Carpet use in living room			
No	31/326 (9.5)	1.00	1.00
Yes	45/539 (8.4)	0.87 (0.54–1.41)	0.84 (0.52–1.39)
Carpet use in maternal bedroom			
No	62/653 (9.5)	1.00	1.00
Yes	14/212 (6.6)	0.67 (0.36–1.20)	0.64 (0.33–1.16)
Vacuuming living room			
Less than 3 times per week	43/370 (11.6)	1.00	1.00
3 times or more per week	33/495 (6.7)	0.54 (0.34–0.87)	0.50 (0.29–0.84)
Vacuuming maternal bedroom			
Less than 3 times per week	51/467 (10.9)	1.00	1.00
3 times or more per week	25/398 (6.3)	0.55 (0.33–0.89)	0.53 (0.31–0.89)
Indoor domestic pets (dogs, cats, birds, or hamsters)			
No	65/755 (8.6)	1.00	1.00
Yes	11/110 (10.0)	1.18 (0.57–2.23)	1.15 (0.55–2.25)
Mold in kitchen			
No	52/684 (7.6)	1.00	1.00
Yes	24/181 (13.3)	1.86 (1.10–3.08)	1.86 (1.08–3.15)
No ducted heating appliance			
No	14/228 (6.1)	1.00	1.00
Yes	62/637 (9.7)	1.65 (0.93–3.12)	1.65 (0.92–3.15)
Gas use for cooking			
No	2/35 (5.7)	1.00	1.00
Yes	74/830 (8.9)	1.62 (0.48–10.08)	1.67 (0.48–10.64)

*Adjustment for maternal age, gestation, family income, maternal and paternal education, maternal and paternal history of asthma, atopic eczema, and allergic rhinitis, time of delivery before second survey, baby's older siblings, baby's sex, and baby's birth weight.
†Antigen levels were semiquantitatively classified with scores of – (<2 $\mu g/m^2$), ± (5 $\mu g/m^2$), + (10–15 $\mu g/m^2$), and ++ (>35 $\mu g/m^2$).

Further adjustment for the mite allergen level from maternal bedclothes during pregnancy did not change the inverse associations of frequent vacuuming the living room and maternal bedroom with the risk of suspected atopic eczema (adjusted ORs: 0.49 and 0.54; 95% CIs: 0.29–0.84 and 0.31–0.92, respectively). After controlling for the mite allergen level from maternal bedclothes during pregnancy, the positive relationship with mold in the kitchen was completely eliminated (adjusted OR: 1.70; 95% CI: 0.97–2.90).

Results for the postnatal home environment are shown in Table 3. Compared with infants who were given a bath or shower less than once a week, those who received a bath or shower at least once a day had a reduced risk of suspected atopic eczema: the multivariate OR was 0.37 (95% CI: 0.17–0.86). No measurable relationships were observed between household smoking in the same room as the infant, infant's synthetic duvet, carpet use in the infant's room, or vacuuming the infant's room and the risk of suspected atopic eczema.

When infants were classified according to whether there was a negative or positive allergic history in at least one parent, positive associations of a high mite allergen level from maternal bedclothes and mold in the kitchen during pregnancy with the risk of suspected atopic eczema were more prominent in infants without a parental allergic history than in those with a parental allergic history (Table 4). Frequent vacuuming of the living room during pregnancy and giving the baby a bath or shower at least once a day were independently related to a decreased risk of suspected atopic eczema only among infants with a positive parental allergic history. An inverse relationship with frequent vacuuming of the maternal bedroom during pregnancy was not statistically significant among infants regardless of parental allergic history. No measurable differences were found in the risk of suspected atopic eczema in relation to these factors between infants with a negative and positive parental allergic history; however ($p = 0.92$, 0.28, 0.90, 0.07, and 0.37 for homogeneity of OR for high mite allergen level from maternal bedclothes, frequent vacuuming of the living room and maternal bedroom, mold in the kitchen, and giving a bath or shower at least once a day, respectively).

Patterns were similar when the definition of the outcome was confined to a definite physician's diagnosis of atopic eczema (n = 42). However, the clear positive association with mold in the kitchen was completely eliminated.

Table 3. Crude and adjusted odds ratios and 95% confidence intervals for suspected atopic eczema in relation to the postnatal home environment in 865 infants, OMCHS, Japan

Home environmental factor	Risk (%)	Crude odds ratio (95% CI)	Adjusted odds ratio (95% CI)*
Household smoking in same room as infant			
No	58/637 (9.1)	1.00	1.00
Yes	18/228 (7.9)	0.86 (0.48–1.46)	0.72 (0.39–1.28)
Infant's synthetic duvet			
No	38/497 (7.7)	1.00	1.00
Yes	38/368 (10.3)	1.39 (0.87–2.23)	1.53 (0.94–2.50)
Carpet use in infant's room			
No	60/648 (9.3)	1.00	1.00
Yes	16/217 (7.4)	0.78 (0.43–1.35)	0.70 (0.38–1.24)
Vacuuming infant's room			
Less than 3 times per week	33/320 (10.3)	1.00	1.00
3 times or more per week	43/545 (7.9)	0.75 (0.46–1.21)	0.75 (0.45–1.23)
Bathing or showering infant			
Less than once a day	9/50 (18.0)	1.00	1.00
At least once a day	67/815 (8.2)	0.41 (0.20–0.93)	0.37 (0.17–0.86)

*Adjustment for maternal age, gestation, family income, maternal and paternal education, maternal and paternal history of asthma, atopic eczema, and allergic rhinitis, time of delivery before second survey, baby's older siblings, baby's sex, and baby's birth weight.

Table 4. Adjusted odds ratios and 95% confidence intervals for suspected atopic eczema in relation to the home environment in 865 infants with a negative or positive parental allergic history, OMCHS, Japan

Home environmental factor	Adjusted odds ratio (95% CI)*	
	Negative parental allergic history (n = 357)	Positive parental allergic history (n = 508)
Mite allergen level from maternal bedclothes†		
–	1.00	1.00
±	0.78 (0.27–2.11)	1.49 (0.67–3.31)
+	1.31 (0.42–3.74)	1.47 (0.58–3.53)
++	4.96 (1.35–17.57)	3.43 (1.17–9.37)
Vacuuming living room		
Less than 3 times per week	1.00	1.00
3 times or more per week	0.68 (0.29–1.61)	0.41 (0.20–0.81)
Vacuuming maternal bedroom		
Less than 3 times per week	1.00	1.00
3 times or more per week	0.53 (0.22–1.22)	0.56 (0.27–1.11)
Mold in kitchen		
No	1.00	1.00
Yes	2.93 (1.27–6.75)	1.23 (0.55–2.56)
Bathing or showering infant		
Less than once a day	1.00	1.00
At least once a day	0.66 (0.18–3.27)	0.26 (0.10–0.77)

*Adjustment for maternal age, gestation, family income, maternal and paternal education, time of delivery before second survey, baby's older siblings, baby's sex, and baby's birth weight.

†Antigen levels were semiquantitatively classified with scores of – (<2 $\mu g/m^2$), ± (5 $\mu g/m^2$), + (10–15 $\mu g/m^2$), and ++ (>35 $\mu g/m^2$).

Discussion

In the present study, a high mite allergen level from maternal bedclothes during pregnancy was

independently associated with an increased risk of suspected atopic eczema. Hagendorens et al. reported that exposure to house dust mites during pregnancy tended to be higher in mothers of children with atopic dermatitis during the first year of life when compared to those without atopic dermatitis among 22 mother–child pairs and that high prenatal exposure to house dust mites was associated with a significantly lower percentage of interferon-γ producing stimulated cord blood CD4+ T lymphocytes (11). Our results are in partial agreement with these findings. The presence of Der p 1 in the amniotic fluid and the fetal circulation was demonstrated (12). Exposure to prenatal house dust mites might influence *in utero* development of immune responses and compromise the postnatal immune deviation process: the Th2 cytokine profile may be boosted during infancy (11).

The current research showed a significant positive relationship between mold in the kitchen during pregnancy and the risk of suspected atopic eczema. The results are partially consistent with a previous cross-sectional study in Japanese adults that found that mold in the kitchen was significantly related to an increased prevalence of elevated serum house dust mite-specific immunoglobulin E (13). There was a strong association between the presence of mold and dampness within a dwelling (14, 15). Thus, dampness in the house could serve as a proxy for the presence of mold. In a cross-sectional study in Italy, both early and current exposure to mold and/or dampness was significantly positively associated with the prevalence of atopic eczema among children, but not adolescents (7). A case–control study in the UK children found a significant positive association between dampness in the house and the risk of current atopic eczema (16). Additional adjustment for the mite allergen level from maternal bedclothes during pregnancy affected the association of mold in the kitchen with the risk of suspected atopic eczema in this study. The positive association with mold in the kitchen may be to some extent attributable to exposure to mite allergen.

Frequent vacuuming of the house, but not the bedroom, was significantly related to an increased risk of lifetime atopic eczema in a previously cited UK case–control study (16). In the present study, further adjustment for the mite allergen level from maternal bedclothes during pregnancy did not measurably influence the beneficial effects of frequent vacuuming of the living room and maternal bedroom during pregnancy. Thus, prenatal exposure to high levels of house dust mites and frequent vacuuming practices during pregnancy were likely to be an independent factors. Although a high mite allergen level from maternal bedclothes was significantly inversely correlated with frequent vacuuming of the living and maternal bedroom (Spearman correlation coefficient, −0.08 and −0.09; $p = 0.02$ and 0.007, respectively), cleaning the maternal bedclothes during pregnancy may be preventive against infantile atopic eczema. However, information on the frequency of cleaning the maternal bedclothes was not available in this study. Alternatively, unrecognized potential allergens or pollutants in floor dust in Japanese homes might have increased risk of infantile atopic eczema.

There was no relationship between indoor domestic pets and the risk of suspected atopic eczema in this study. Our results are in partial agreement with previous epidemiologic studies that showed no relationship between domestic pets and atopic eczema (17–19). A cohort study in Germany found a significant beneficial association of keeping pets, especially dogs, in the first year of life with the development of atopic dermatitis in the first and second years of life (6). A significant inverse relationship between current cat ownership and the prevalence of atopic dermatitis was reported in Japanese schoolchildren (20). According to the hygiene hypothesis, indoor domestic pets in early life, but not during pregnancy, would be preventive against atopic eczema if domestic pets contribute to the infectious effect by carrying high levels of several biologically active components or other infectious agents into the home.

A prospective cohort study in Denmark showed no statistically significant association between any *in utero* smoke exposure and the risk of atopic eczema (21). Some epidemiologic studies found no material relationship between passive smoking and atopic eczema in children (17, 19, 20, 22). Our results regarding maternal smoking during pregnancy and postnatal passive smoking are consistent with these observations. A significant positive relationship of maternal smoking during pregnancy and lactation to the prevalence of atopic eczema was demonstrated among German children, however (23). Our findings in relation to gas use for cooking and having no ducted heating system are in partial agreement with previous studies showing no relationship of gas use for heating or cooking to atopic eczema in children (16, 22) but are inconsistent with an observation showing a positive association with indoor use of gas without hood (5).

The possible protective effect of bathing or showering the infant at least once a day has been identified. In particular, risk of suspected atopic eczema was significantly reduced by 74% among infants with a positive parental allergic history. A recommendation to give an infant a bath or shower every day might be made to parents with an allergic history for prevention of infantile atopic eczema. To our knowledge, there is no evidence regarding the association between bathing or showering practices and the risk of atopic eczema in infants. More research on this issue is needed.

The current investigation had several methodological advantages in that the prospective design and relatively high rate of follow up (86.3%) minimized the possibility of recall bias or bias caused by loss of follow up and in that study subjects were homogeneous in terms of having the same residential background. We also incorporated extensive information on confounding factors.

Important weaknesses in the present study should be taken into consideration when interpreting our results. The second survey was conducted at 2–9 months postpartum although 89.2% of the subjects took part in the second survey at 3–4 months postpartum. Because it is difficult to assess the development of infantile atopic eczema accurately, we used the term 'suspected atopic eczema' as the definition of outcome based on our questionnaire in the second survey. The resulting bias would have driven the estimated effects toward the null value due to non-differential outcome misclassification.

In the baseline survey, the participation rate was low in Neyagawa City (17.2%). We were not able to evaluate the difference between participants and non-participants in Neyagawa City, because data on personal characteristics among the non-participants were not available. Moreover, we were not able to calculate the participation rate of subjects from other areas nor were data available on the non-participants in those areas. The mothers in our population were an unrepresentative sample of Japanese females in the general population, and the present findings may not be generalized. In fact, educational levels were higher in the present study population than in the general population. According to the 2000 population census of Japan, the proportions of females aged 30–34 yr in Osaka Prefecture with years of education of < 13, 13–14, 15+, and unknown were 49.2%, 32.3%, 13.6%, and 4.9%, respectively. The corresponding figures for the current study were 29.7%, 42.4%, 27.9%, and 0.0%, respectively. The lifetime prevalence of atopic eczema might be higher among our parents than among the general population. Muto et al. (24) reported that the lifetime prevalence of atopic eczema was 4.2% and 4.4%, respectively, for Japanese men and women aged 30–39 yr according to UK Working Party's diagnostic criteria. On the other hand, the prevalence of atopic eczema might be lower among our infants than among the general population. Another paper in Japan showed that eczema was observed in 30% of the 4-month-old infants who came to public health examinations (25).

In conclusion, the current prospective study found that among Japanese infants, a high mite allergen level from maternal bedclothes and mold in the kitchen during pregnancy were significantly associated with an increased risk of suspected atopic eczema, whereas frequent vacuuming practices during pregnancy and giving the infant a bath or shower at least once a day were significantly inversely related to the risk of suspected atopic eczema. Further follow up of our cohort will show whether the detrimental effects of mite allergen and mold during pregnancy and the beneficial effects of vacuuming practices, bathing, and showering persist into childhood.

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Appendix

Space limitations preclude the inclusion as authors of the following members of the Osaka Maternal and Child Health Study Group:

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PEDIATRIC ALLERGY AND IMMUNOLOGY

Cross-sectional study of allergic disorders associated with breastfeeding in Japan: The Ryukyus Child Health Study

Miyake Y, Arakawa M, Tanaka K, Sasaki S, Ohya Y. Cross-sectional study of allergic disorders associated with breastfeeding in Japan: The Ryukyus Child Health Study.
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Uncertainties remain as to whether breastfeeding is protective against childhood allergic disorders. Positive relationships of breastfeeding with asthma and atopic eczema were observed in two previous Japanese studies. This cross-sectional study investigated the association between the feeding pattern after birth and the prevalence of allergic disorders during the past 12 months in Japanese schoolchildren. Study subjects were 24,077 children aged 6–15 yr in Okinawa. The outcomes were based on diagnostic criteria from the International Study of Asthma and Allergies in Childhood. Allowance was made for age, sex, number of siblings, smoking in the household, paternal and maternal history of asthma, atopic eczema, and allergic rhinitis, and paternal and maternal educational level. Breastfeeding, regardless of exclusivity, for 13 months or longer and exclusive breastfeeding for 4–11 months were independently associated with a higher prevalence of atopic eczema, particularly among children without a parental allergic history. A clear positive dose–response relationship was observed between prolonged duration of breastfeeding, regardless of exclusivity, but not exclusive breastfeeding, and the prevalence of atopic eczema. We found a significant positive trend for atopic eczema across the three categories (formula milk, partial and exclusive breastfeeding) in the first 4 months of life although the odds ratio for exclusive breastfeeding was not statistically significant. No material association was found between the feeding pattern after birth and the prevalence of wheeze or allergic rhinoconjunctivitis. Prolonged breastfeeding may be associated with a higher prevalence of atopic eczema in Japanese children.

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Key words: allergic rhinoconjunctivitis; atopic eczema; breastfeeding; cross-sectional study; Japanese children; wheeze

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Uncertainties remain as to whether breastfeeding is protective against childhood allergic disorders. A prospective birth cohort study in Sweden showed that exclusive breastfeeding for 4 months or more reduced the risk of infantile asthma, atopic eczema, and suspected allergic rhinitis (1–3). Exclusive breastfeeding for at least 4 months was significantly associated with a decreased risk of childhood asthma and positive skin prick test results in an Australian prospective study (4). On the other hand, some epidemiological investigations were not able to substantiate such a protective association (5–8). Moreover, in a New Zealand birth cohort, breastfeeding for 4 wk or longer was significantly related to an increased risk of positive skin test responses at age 13 yr and asthma throughout childhood and adulthood (9). Two cohort studies found a positive association between a longer duration of breastfeeding and the risk of atopic eczema in children (10, 11). Breastfeeding raised the risk of atopic eczema only in infants without a parental history of allergy in two prospective studies (12, 13). However, a multidisciplinary review

concluded that breastfeeding seems to protect against development of allergic disease, especially among children with an atopic heredity (14). Similar conclusions were drawn in three systematic reviews with meta-analysis of prospective studies (15–17).

To our knowledge, only two epidemiological studies assessed the relationship between breastfeeding and allergic disorders in Japan (18, 19). Breastfeeding was significantly related to a higher prevalence of asthma in a population-based case–control study among children aged 6–15 yr (18). A cross-sectional study of Japanese adolescents found a significant positive association of breastfeeding with the prevalence of atopic eczema, but not asthma and allergic rhinoconjunctivitis, particularly among children without a parental allergic history (19). These adverse reports prompted us to further investigate the issue using data from the Ryukyus Child Health Study (RYUCHS). Our aim was to examine whether breastfeeding is associated with a higher prevalence of childhood allergic disorders, using the diagnostic criteria of the International Study of Asthma and Allergies in Childhood (ISAAC).

Methods

Study population

Okinawa Prefecture is an island located in the southernmost area in Japan, with a subtropical climate and a total population of almost 1,360,000. Naha City, the largest city in Okinawa Prefecture and located in the south of the island, and Nago City, located in the center of the island, with a total population of almost 311,000 and 58,000, respectively, are two of the 41 municipalities in Okinawa Prefecture. All 35 public elementary schools and 17 junior high schools in Naha City and all 17 public elementary schools and eight junior high schools in Nago City participated in the RYUCHS during the period from September 2004 to January 2005. The purpose of the RYUCHS, which was a cross-sectional survey, was to investigate the associations between various selected factors and child health problems. A set of two self-administered questionnaires was distributed by teachers to all 38,212 schoolchildren aged 6–15 yr. The questionnaires were answered by the parents of the elementary schoolchildren and the junior high school students themselves and/or their parents. When research technicians found missing or illogical data, the teachers sent the questionnaires back to the parents. Finally, 28,885 sets of the questionnaires (75.6%) were returned. A total of 4808 children were excluded because of missing or illogical data on the factors under investigation. The final analysis comprised 24,077 subjects (63.0%). The ethics committee of the Faculty of Medicine, Fukuoka University approved the RYUCHS.

Measurements

One of the self-administered questionnaires included questions on symptoms of wheeze, atopic eczema, and allergic rhinoconjunctivitis in the past 12 months based on the validated ISAAC phase-I questionnaire, which has been reported in detail elsewhere (20–23). We translated these questions into Japanese by using standard forward–backward translation. Wheeze was considered to be present if respondents answered 'yes' to the written question 'Have you (Has your child) had wheezing or whistling in the chest in the last 12 months?'. Those children with a positive response to questioning about the presence of an itchy relapsing skin rash that had affected their skin creases in the past 12 months were considered to have atopic eczema. Rhinoconjunctivitis was defined as a positive response to both questions 'In the past 12 months, have you (has your child) had a problem with sneezing or a runny or blocked nose, when you (he or she) did not have a cold or the flu?' and 'In the past 12 months, has this nose problem been accompanied by itchy-watery eyes?' The questionnaire also elicited information on age, sex, number of siblings, smoking in the household, paternal and maternal history of asthma, atopic eczema, and allergic rhinitis, paternal and maternal educational level, breastfeeding duration in months, and the age in months at which formula milk was introduced. Exposure to formula milk in the delivery hospitals was not taken into consideration. A paternal or maternal history of asthma, atopic eczema, and allergic rhinitis was defined as positive if the respective parent had contracted any of these allergic disorders since the parent's birth.

The other instrument was a validated self-administered brief diet history questionnaire. Data regarding diet were not used in the current study.

Statistical analysis

Logistic regression analysis was used to estimate crude odds ratios (ORs) and their 95% confidence intervals (CIs). Also, multiple logistic

regression analysis was used to control for the potential confounding effects of selected factors. Trend of association was assessed by a logistic regression model assigning consecutive integers to the levels of the independent variable. Two-sided p-values <0.05 were regarded as statistically significant. All computations were performed using the SAS software package, version 9.1 (SAS Institute, Inc., Cary, NC, USA).

Age, sex, number of siblings, smoking in the household, paternal and maternal history of asthma, atopic eczema, and allergic rhinitis, and paternal and maternal educational level were statistically significantly related to any of the three outcomes under study and were selected as confounding factors. Age was classified into three categories (6–8, 9–11, and 12–15 yr), number of siblings into four (0, 1, 2, and 3+), smoking in the household into three according to whether children had lived with at least one smoker (never, former, and current), paternal and maternal educational level into four (junior high school, high school, junior college or vocational technical school, and university), feeding pattern in the first 4 months of life into three (formula milk, partial breastfeeding and exclusive breastfeeding), duration of breastfeeding, regardless of exclusivity into four (<4, 4–6, 7–12, and 13+ months), duration of exclusive breastfeeding into four (<1, 1–3, 4–11, and 12+ months) and introduction of formula milk into four (none, 4+, 1–3, and 0 months).

Table 1. Distribution of selected characteristics in 24,077 schoolchildren, RYUCHS, Japan

Variable	n (%)
Male sex	11,916 (49.5)
Age (yr)	
6–8	7269 (30.2)
9–11	8678 (36.0)
12–15	8130 (33.8)
Siblings	
0	2206 (9.2)
1	8152 (33.9)
2	9091 (37.8)
3+	4628 (19.2)
Smoking in household	
Never	10,394 (43.2)
Former	2457 (10.2)
Current	11,226 (46.6)
Paternal history of asthma	1665 (6.9)
Paternal history of atopic eczema	657 (2.7)
Paternal history of allergic rhinitis	4187 (17.4)
Maternal history of asthma	2039 (8.5)
Maternal history of atopic eczema	1067 (4.4)
Maternal history of allergic rhinitis	5267 (21.9)
Paternal educational level	
Junior high school	1840 (7.6)
High school	10,631 (44.2)
Junior college or vocational technical school	3588 (14.9)
University	8018 (33.3)
Maternal educational level	
Junior high school	1175 (4.9)
High school	10,584 (44.0)
Junior college or vocational technical school	10,130 (42.1)
University	2188 (9.1)
Feeding pattern in the first 4 months of life	
Formula milk	1588 (6.6)
Partial breastfeeding	13,994 (58.1)
Exclusive breastfeeding	8495 (35.3)

Results

In the current study, the prevalence values of symptoms of wheeze, atopic eczema, and allergic rhinoconjunctivitis in the past 12 months were 10.8%, 6.9%, and 7.7%, respectively. Table 1 gives the distribution of selected factors among the 24,077 subjects. Approximately 60% of the subjects had two or more siblings. About half had at least one current smoker in the household. Many more children had parents with a history of allergic rhinitis than parents with a history of asthma or atopic eczema. About 60% had received formula milk in addition to breast milk whereas only 7% had consumed formula milk exclusively in the first 4 months of life.

Table 2 presents crude and adjusted ORs and their 95% CIs for allergic disorders in relation to the feeding pattern in the first 4 months of life. Compared with formula milk, partial and exclusive breastfeeding was not significantly associated with the prevalence of atopic eczema although a significant positive trend across the three categories of the feeding pattern was found. After adjustment for age, sex, number of siblings, smoking in the household, paternal and maternal history of asthma, atopic eczema, and allergic rhinitis, and paternal and maternal educational level, the positive trend remained statistically significant (p for trend = 0.04). No measurable relationship was observed between the feeding pattern in the first 4 months of life and the prevalence of wheeze or allergic rhinoconjunctivitis.

Table 3 provides crude and adjusted ORs and 95% CIs according to duration of breastfeeding, regardless of exclusivity. Breastfeeding, regardless of exclusivity, for 13 months or more was significantly associated with a higher prevalence of atopic eczema. The positive dose–response relationship between prolonged breastfeeding duration, regardless of exclusivity, and the prevalence of atopic eczema was statistically significant. Adjustment for confounders under study did not appreciably change the results: the multivariate OR for 13 months or more vs.

Table 2. Odds ratios and 95% confidence intervals for allergic disorders according to feeding pattern in the first 4 months of life in 24,077 schoolchildren, RYUCHS, Japan

Feeding pattern	Prevalence	Crude OR (95% CI)	Adjusted OR (95% CI)*
Wheeze			
Formula milk	181/1588 (11.4%)	1.00	1.00
Partial breastfeeding	1526/13994 (10.9%)	0.95 (0.81–1.12)	0.92 (0.78–1.10)
Exclusive breastfeeding	886/8495 (10.4%)	0.91 (0.77–1.08)	0.93 (0.79–1.11)
p for trend		0.16	0.74
Atopic eczema			
Formula milk	97/1588 (6.1%)	1.00	1.00
Partial breastfeeding	949/13994 (6.8%)	1.12 (0.91–1.40)	1.08 (0.87–1.35)
Exclusive breastfeeding	620/8495 (7.3%)	1.21 (0.98–1.52)	1.19 (0.95–1.50)
p for trend		0.05	0.04
Allergic rhinoconjunctivitis			
Formula milk	120/1588 (7.6%)	1.00	1.00
Partial breastfeeding	1095/13994 (7.8%)	1.04 (0.86–1.27)	1.02 (0.84–1.25)
Exclusive breastfeeding	646/8495 (7.6%)	1.01 (0.83–1.24)	1.00 (0.81–1.23)
p for trend		0.74	0.79

*Adjustment for age, sex, number of siblings, smoking in the household, paternal and maternal history of asthma, atopic eczema, and allergic rhinitis, and paternal and maternal educational level.

Table 3. Odds ratios and 95% confidence intervals for allergic disorders according to duration of breastfeeding, regardless of exclusivity, in 24,077 schoolchildren, RYUCHS, Japan

Duration of breastfeeding, regardless of exclusivity	Prevalence	Crude OR (95% CI)	Adjusted OR (95% CI)*
Wheeze			
<4 months	1000/9016 (11.1%)	1.00	1.00
4–6 months	573/5618 (10.2%)	0.91 (0.82–1.01)	0.95 (0.85–1.06)
7–12 months	634/5851 (10.8%)	0.97 (0.88–1.08)	1.05 (0.94–1.17)
13+ months	386/3592 (10.8%)	0.97 (0.85–1.09)	1.03 (0.91–1.17)
p for trend		0.61	0.39
Atopic eczema			
<4 months	589/9016 (6.5%)	1.00	1.00
4–6 months	379/5618 (6.8%)	1.04 (0.91–1.18)	1.04 (0.91–1.19)
7–12 months	423/5851 (7.2%)	1.12 (0.98–1.27)	1.11 (0.98–1.27)
13+ months	275/3592 (7.7%)	1.19 (1.02–1.38)	1.18 (1.01–1.37)
p for trend		0.01	0.02
Allergic rhinoconjunctivitis			
<4 months	690/9016 (7.7%)	1.00	1.00
4–6 months	438/5618 (7.8%)	1.02 (0.90–1.16)	1.03 (0.91–1.17)
7–12 months	430/5851 (7.4%)	0.96 (0.84–1.08)	0.96 (0.84–1.09)
13+ months	303/3592 (8.4%)	1.11 (0.96–1.28)	1.13 (0.98–1.30)
p for trend		0.43	0.35

*Adjustment for age, sex, number of siblings, smoking in the household, paternal and maternal history of asthma, atopic eczema, and allergic rhinitis, and paternal and maternal educational level.

< 4 months of breastfeeding duration, regardless of exclusivity, was 1.18 (95% CI, 1.01–1.37, p for trend = 0.02). There was no material relationship between breastfeeding duration, regardless of exclusivity, and the prevalence of wheeze or allergic rhinoconjunctivitis.

ORs for associations between duration of exclusive breastfeeding and allergic disorders are shown in Table 4. Regarding atopic eczema, the multivariate OR for comparison of 4–11 months, but not 1–3 months or 12 months or more, with < 1 month of exclusive breastfeeding duration was statistically significant. However, no evident positive dose–response relationship with exclusive breastfeeding duration was found. Exclusive breastfeeding duration was not significantly associated with the prevalence of wheeze or allergic rhinoconjunctivitis.

Results for the introduction of formula milk are given in Table 5. We found no statistically significant relationship of the age in months at which formula milk was introduced with the prevalence of any of the allergic disorders in the multivariate model.

When stratifying the children according to whether there was a positive or negative allergic

Table 4. Odds ratios and 95% confidence intervals for allergic disorders according to duration of exclusive breastfeeding in 24,077 schoolchildren, RYUCHS, Japan

Duration of exclusive breastfeeding	Prevalence	Crude OR (95% CI)	Adjusted OR (95% CI)*
Wheeze			
<1 month	1287/11593 (11.1%)	1.00	1.00
1–3 months	546/5293 (10.3%)	0.92 (0.83–1.02)	0.96 (0.87–1.07)
4–11 months	457/4131 (11.1%)	1.00 (0.89–1.12)	1.07 (0.95–1.20)
12+ months	303/3060 (9.9%)	0.88 (0.77–1.00)	0.95 (0.83–1.09)
p for trend		0.12	0.94
Atopic eczema			
<1 month	788/11593 (6.8%)	1.00	1.00
1–3 months	338/5293 (6.4%)	0.94 (0.82–1.07)	0.98 (0.86–1.12)
4–11 months	318/4131 (7.7%)	1.14 (1.00–1.31)	1.18 (1.03–1.35)
12+ months	222/3060 (7.3%)	1.07 (0.92–1.25)	1.09 (0.93–1.28)
p for trend		0.11	0.05
Allergic rhinoconjunctivitis			
<1 month	946/11593 (8.2%)	1.00	1.00
1–3 months	375/5293 (7.1%)	0.86 (0.76–0.97)	0.89 (0.78–1.01)
4–11 months	300/4131 (7.3%)	0.88 (0.77–1.01)	0.89 (0.78–1.02)
12+ months	240/3060 (7.8%)	0.96 (0.83–1.11)	0.98 (0.84–1.13)
p for trend		0.16	0.29

*Adjustment for age, sex, number of siblings, smoking in the household, paternal and maternal history of asthma, atopic eczema, and allergic rhinitis, and paternal and maternal educational level.

Table 5. Odds ratios and 95% confidence intervals for allergic disorders according to introduction of formula milk in 24,077 schoolchildren, RYUCHS, Japan

Introduction of formula milk	Prevalence	Crude OR (95% CI)	Adjusted OR (95% CI)*
Wheeze			
None	364/3695 (9.9%)	1.00	1.00
4+ months	526/4818 (10.9%)	1.12 (0.97–1.29)	1.08 (0.93–1.24)
1–3 months	606/5708 (10.6%)	1.09 (0.95–1.25)	1.02 (0.89–1.18)
0 month	1097/9856 (11.1%)	1.15 (1.01–1.30)	1.04 (0.92–1.19)
p for trend		0.07	0.80
Atopic eczema			
None	274/3695 (7.4%)	1.00	1.00
4+ months	347/4818 (7.2%)	0.97 (0.82–1.14)	0.97 (0.82–1.14)
1–3 months	371/5708 (6.5%)	0.87 (0.74–1.02)	0.88 (0.74–1.03)
0 month	674/9856 (6.8%)	0.92 (0.79–1.06)	0.89 (0.77–1.03)
p for trend		0.18	0.07
Allergic rhinoconjunctivitis			
None	292/3695 (7.9%)	1.00	1.00
4+ months	355/4818 (7.4%)	0.93 (0.79–1.09)	0.92 (0.78–1.08)
1–3 months	407/5708 (7.1%)	0.90 (0.77–1.05)	0.90 (0.77–1.06)
0 month	807/9856 (8.2%)	1.04 (0.91–1.20)	1.01 (0.88–1.17)
p for trend		0.28	0.48

*Adjustment for age, sex, number of siblings, smoking in the household, paternal and maternal history of asthma, atopic eczema, and allergic rhinitis, and paternal and maternal educational level.

history in at least one parent, positive associations of exclusive breastfeeding in the first 4 months of life and prolonged breastfeeding duration with the prevalence of atopic eczema were more evident in children without a parental allergic history than in those with a parental allergic history (Table 6). No measurable differences were observed in the prevalence of atopic eczema between children with a positive and negative parental allergic history ($p = 0.82$, 0.86, 0.74, 0.64, 0.11, 0.76, 0.16, and 0.96 for homogeneity of OR for partial and exclusive breastfeeding in the first 4 months of life, 4–6 months, 7–12 months, and 13 months or more of breastfeeding duration, regardless of exclusivity, and 1–3 months, 4–11 months, and 12 months or more of exclusive breastfeeding duration, respectively).

Discussion

The present cross-sectional study demonstrated that breastfeeding, regardless of exclusivity, for 13 months or longer and exclusive breastfeeding for 4–11 months were independently associated

Table 6. Adjusted odds ratios and 95% confidence intervals for atopic eczema according to infant feeding variables in 24,077 schoolchildren with a positive or negative parental allergic history, RYUCHS, Japan

Feeding variable	Adjusted OR (95% CI)*	
	Positive parental allergic history (n = 10,210)	Negative parental allergic history (n = 13,867)
Feeding pattern in the first 4 months of life		
Formula milk	1.00	1.00
Partial breastfeeding	1.09 (0.83–1.46)	1.03 (0.75–1.47)
Exclusive breastfeeding	1.16 (0.87–1.57)	1.22 (0.87–1.74)
p for trend	0.24	0.06
Duration of breastfeeding, regardless of exclusivity		
<4 months	1.00	1.00
4–6 months	1.04 (0.88–1.23)	1.00 (0.80–1.24)
7–12 months	1.09 (0.92–1.29)	1.17 (0.95–1.45)
13+ months	1.07 (0.87–1.30)	1.39 (1.09–1.75)
p for trend	0.36	0.005
Duration of exclusive breastfeeding		
<1 month	1.00	1.00
1–3 months	0.98 (0.83–1.16)	0.95 (0.76–1.17)
4–11 months	1.08 (0.90–1.29)	1.32 (1.07–1.63)
12+ months	1.09 (0.89–1.33)	1.12 (0.86–1.43)
p for trend	0.30	0.06

*Adjustment for age, sex, number of siblings, smoking in the household, and paternal and maternal educational level.

with a higher prevalence of atopic eczema, particularly among children without a parental allergic history. A clear positive dose–response relationship was observed between prolonged duration of breastfeeding, regardless of exclusivity, but not exclusive breastfeeding, and the prevalence of atopic eczema. We found a significant positive trend for atopic eczema across the three categories of feeding pattern in the first 4 months of life although the multivariate OR for comparison of exclusive breastfeeding with formula milk in the first 4 months of life was not statistically significant. No material association was found between the feeding pattern after the birth and the prevalence of wheeze or allergic rhinoconjunctivitis. These results are in partial agreement with previous epidemiological studies showing a positive association between breastfeeding and childhood atopic eczema (10–13, 19) and no relationship between breastfeeding and asthma (6–8) or allergic rhinoconjunctivitis (19).

Okinawa is known to have the highest longevity rate and lowest mortality rate from cardiovascular and cerebrovascular diseases and cancer in Japan (24). The distribution of various environmental factors in Okinawa is likely to be different from that in the mainland of Japan. In fact, the prevalence of allergic disorders in the current study was quite different from that in the mainland of Japan. According to another cross-sectional study among Japanese adolescents in Suita City in an urban area of the mainland, the prevalence values for symptoms of wheeze, atopic eczema, and allergic rhinoconjunctivitis in the past 12 months were 6.7%, 14.5%, and 23.9%, respectively, by using the ISAAC criteria (19). Both the studies in the present population and in Suita City showed a significant positive association between breastfeeding and atopic eczema, although the positive association with exclusive breastfeeding in the first 4 months of life was more pronounced in the Suita study than in this study (19). The difference in prevalence of atopic eczema between Okinawa and Suita may be to some extent attributable to concentrations of unknown active substances in breast milk.

Dioxins are among the possible active agents in human milk. A study in Japanese women showed that the levels of polychlorinated dibenzo-*p*-dioxins, polychlorinated dibenzofurans, and coplanar polychlorinated biphenyls in breast milk were higher in primiparae than in secundiparae and that the levels were lower in secundiparae who had breastfed their first babies than in those who bottle-fed or partly bottle-fed their first born (25). In Dutch children at 3.5 yr, the plasma levels of polychlorinated biphenyls were 3.6 times higher in breast-fed infants than in bottle-fed infants and the breastfeeding period and breast milk polychlorinated biphenyl levels were important predictors for polychlorinated biphenyl levels in the breast-fed group (26). In Japanese breast-fed infants, the $CD4^+$ and $CD8^+$ counts and the ratio between the two lymphocyte subsets were shown to be influenced by dioxins (27). A positive association between raised blood levels of polychlorinated dibenzo-*p*-dioxins and polychlorinated dibenzofurans and a history of allergy was observed in Japanese workers exposed to a large amount of dioxins (28). However, a study among 8-yr-old Dutch children revealed a decrease in allergy in relation to pre-natal and post-natal dioxin exposure although the definition of the outcome was crude and there was no relationship of such exposure with a history of asthma and eczema (29). A laboratory study demonstrated that 2,3,7,8-tetrachlorodibenzo-*p*-dioxin enhanced spontaneous IgE production in B cells from Japanese atopic patients (30).

According to the hygiene hypothesis, early infections may be important for development of mature immune responses. Breastfeeding might alleviate the impact of immune stimulants such as bacteria and endotoxins. The Danish National Birth Cohort showed a significant positive association between exclusive breastfeeding at 4 months of age and atopic eczema in children of

non-allergic parents after adjustment for the number of early infections occurring before 6 months of age, however (12). Although we could not assess this assumption because data on early infections were not available in the present study, this assumption is also likely to be at variance with our findings on lack of a significant association between breastfeeding and the prevalence of wheeze and allergic rhinocon junctivitis.

Weakness of the current cross-sectional study should be borne in mind when interpreting our results. Nevertheless, the present study had several methodological advantages. As the outcomes under investigation were estimated by using the validated ISAAC-based questions, some limitations in relation to a questionnaire-based evaluation were likely to be mitigated. Study subjects were homogeneous with respect to age and geographical background. The large number of subjects and variables allowed us to overcome the problems such as small sample size, inadequate data on potential confounders, and reduced statistical power. However, in the present study no allowance was made for external factors such as food allergens, toxic chemicals, and water hardness in the present study.

As 63.0% of the eligible subjects were included in this analysis, selection bias was not likely to be negligible. Compared with 4808 participants who were excluded because of incomplete data but who did answer questions on the following issues, 24,077 study subjects were less likely to have no siblings, former smokers in the household, mothers with a history of asthma, and mothers who had stopped breastfeeding within the first 4 months of life, and were more likely to be male and young, and have a personal history of atopic eczema and allergic rhinoconjunctivitis, family members who had never smoked, fathers with a history of atopic eczema and allergic rhinitis, and both fathers and mothers with a high educational level. There was no statistically significant difference between the excluded participants and study subjects regarding the prevalence of wheeze, introduction of formula milk, a paternal history of asthma, and a maternal history of atopic eczema and allergic rhinitis. In particular, 2529 participants and 2368 participants were excluded because they did not reply to the question regarding a paternal allergic history and educational level, respectively. If the proportions of children with atopic eczema and those who had been breastfed for a prolonged period among study subjects were higher than among the excluded participants and non-participants, the reported ORs for atopic eczema would have been overestimated. Study subjects in Okinawa may differ from Japanese children in the general population in terms of allergic history and lifestyle characteristics. Thus, we should be cautious in generalizing the current findings.

Recall bias associated with the feeding pattern after birth should be discussed. Parents, particularly those with an older child, might not have been able to remember specific details about duration and exclusivity of breastfeeding. Parents of children with allergic disorders might have reported a longer duration of breastfeeding than actually occurred. This type of differential exposure misclassification could lead to bias toward a positive direction. Mothers of children with atopic eczema that developed during the breastfeeding period actually might have tried to continue breastfeeding compared with mothers of children without atopic eczema. The consequence would have given rise to an overestimation of the results regarding atopic eczema. If wheeze and allergic rhinoconjunctivitis had a later onset, the choice of feeding pattern after birth could not be influenced. One possibility is that parents choose to breastfeed longer if they have a history of allergic disorders. However, in this study, there was no relationship between the presence of parental allergic history and breastfeeding duration and a positive association between breastfeeding and atopic eczema was evident among children without a parental allergic history. Thus, the impact of this possibility is likely to be minor.

In conclusion, the present study found a significant positive association of prolonged breastfeeding with the prevalence of atopic eczema, especially among children without a parental allergic history in a rural area in Japan. Similar results were demonstrated in another previous Japanese cross-sectional study in an urban area. We have no clear explanation as to the underlying mechanisms for the positive association between breastfeeding and atopic eczema. The nature of cross-sectional studies prevents conclusions from being drawn about causality. There is a need for prospective cohort studies to evaluate the association between breastfeeding and allergic disorders in Japan.

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