

Breastfeeding and atopic eczema in Japanese infants: The Osaka Maternal and Child Health Study

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Epidemiological studies associated with breastfeeding have provided conflicting results about whether it is preventive or a risk factor for atopic eczema in children. The current prospective study investigated the relationship between breastfeeding and the risk of atopic eczema in Japan. A birth cohort of 763 infants was followed. The first survey during pregnancy and the second survey between 2 and 9 months postpartum collected information on potential confounding factors and atopic eczema status. Data on breastfeeding and symptoms of atopic eczema were obtained from questionnaires in the third survey from 16 to 24 months postpartum. The following variables were *a priori* selected as potential confounders: maternal age, maternal and paternal history of asthma, atopic eczema, and allergic rhinitis, indoor domestic pets (cats, dogs, birds, or hamsters), family income, maternal and paternal education, maternal smoking during pregnancy, baby's sex, baby's birth weight, baby's older siblings, household smoking in the same room as the infant, and time of delivery before the third survey. In the third survey, 142 infants (18.6%) were revealed to have developed atopic eczema based on criteria of the International Study of Asthma and Allergies in Childhood. In an overall analysis, neither exclusive nor partial breastfeeding was significantly related to the risk of atopic eczema. After excluding 64 infants identified with suspected atopic eczema in the second survey, both exclusive breastfeeding for 4 months or more and partial breastfeeding for 6 months or more were independently associated with an increased risk of atopic eczema only among infants with no parental history of allergic disorders [multivariate odds ratios were 2.41 (95% confidence interval, 1.10–5.55) and 3.39 (95% confidence interval, 1.20–12.36), respectively]. The authors found that, overall, neither exclusive nor partial breastfeeding had a strong impact on the risk of atopic eczema. However, a parental allergic history may affect the risk.

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Epidemiological studies of associations with breastfeeding have provided conflicting results about whether breastfeeding is preventive or a risk factor for atopic eczema in children. A prospective cohort study among Swedish children showed that exclusive breastfeeding for 24 months or more reduced the risk of atopic

eczema, especially of eczema during the first 2 yr, persisting to 4 yr (1, 2). The German Infant Nutritional Intervention Program found that, compared with conventional cow's milk formula in the first 4 months of life, exclusive breastfeeding was significantly associated with a decreased risk of atopic eczema only in children in the

interventional subgroup with a parental allergic history (3). Two cohort studies observed no relationship between duration of breastfeeding and the risk of atopic eczema in the first 1 yr of life (4, 5). A longer duration of breastfeeding was related to an increased risk of atopic eczema in children in two prospective studies (6, 7). Exclusive breastfeeding for 9 months or more was associated with atopic eczema at age 5 yr, but not at ages 11 and 20 yr (8). Two prospective studies showed a positive association between breastfeeding and atopic eczema only in infants without a parental allergic history (9, 10). In two cross-sectional studies among Japanese children, breastfeeding was related to an increased prevalence of atopic eczema (11, 12). However, meta-analysis of prospective studies demonstrated that exclusive breastfeeding during the first 3 months of life was inversely associated with the risk of atopic eczema during childhood (13). A large cluster-randomized trial in the Republic of Belarus demonstrated that an intervention of breastfeeding promotion decreased the risk of atopic eczema in the first year of life (14). In view of the absence of prospective studies of the relationship between breastfeeding and atopic eczema in Japan, the aim of the current study was to investigate the association between breastfeeding and the risk of atopic eczema among Japanese infants 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 examines 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 (Fig. 1). 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 women were those 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 *c.* 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 envelope 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. In addition, 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. The second survey was carried out from 2 to 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, 7, 8, or 9 months postpartum. Of the 867 mothers, 763 took part in the third survey from 16 to 24 months postpartum. Data on 763 mother-child pairs were used for the analysis. The ethics committee of the Osaka City University School of Medicine approved the OMCHS.

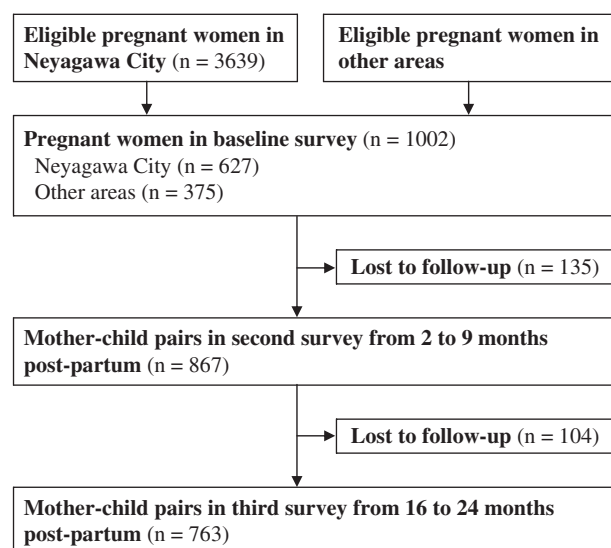


Fig. 1. Eligibility for and participation in the Osaka Maternal and Child Health Study.

Measurements

At baseline, each participant filled out a set of two self-administered questionnaires. A self-administered questionnaire was also used in both the second and third survey. Participants mailed these materials to the data management center. Research technicians completed missing or illogical data by telephone interview.

In the baseline survey, a questionnaire inquired about maternal age, family income, maternal and paternal education, maternal and paternal history of asthma, atopic eczema, and allergic rhinitis, and indoor domestic pets. 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.

A self-administered questionnaire in the second survey elicited information on maternal smoking during pregnancy, 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 after birth, and atopic eczema status. In the second survey, 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 ($n = 23$ of 763 participants in the third survey); (ii) my child has been diagnosed with atopic eczema but has not been treated with topical steroids ($n = 12$); (iii) my child has been diagnosed with atopic eczema and treated with an unknown ointment ($n = 1$); (iv) my child has been diagnosed as possibly having atopic eczema and has been treated with topical steroids ($n = 27$); or (v) my child has been diagnosed as possibly having atopic eczema but has not been treated with topical steroids ($n = 1$).

A self-administered questionnaire in the third survey included questions on breastfeeding duration in months, the age in months at which formula milk and solid foods were introduced, and symptoms of atopic eczema based on the International Study of Asthma and Allergies in Childhood (ISAAC) phase-I questionnaire. The mothers were asked (i) 'Have you breastfed?' and, if 'yes', 'Are you still breastfeeding?' and, if 'no', 'What was your baby's age in months when you

stopped breastfeeding?'; (ii) 'Do you give your infant formula milk?' and, if 'yes', 'What was your baby's age in months when you began to give your infant formula milk?'; and (iii) 'What was your baby's age in months when you began giving your infant solid foods?'. Exclusive breastfeeding duration was defined as the period when the infants were given only breast milk, and formula milk or solid foods had not been introduced. Partial breastfeeding duration was the period when the infants had received breast milk, regardless of exclusivity. For atopic eczema, affirmative answers to the following three questions in the ISAAC questionnaire 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 elbow, behind the knees, in front of the ankles, under the buttocks, or around the neck, ears, or eyes?'

Statistical analysis

Logistic regression analysis was used to estimate crude odds ratios (ORs) and 95% confidence intervals (CIs) for atopic eczema relative to breastfeeding duration. Multiple logistic regression analysis was employed to control for the effects of confounding variables. The following variables were *a priori* selected as potential confounders: maternal age, maternal and paternal history of asthma, atopic eczema, and allergic rhinitis, indoor domestic pets (cats, dogs, birds, or hamsters), family income, maternal and paternal education, maternal smoking during pregnancy, baby's sex, baby's birth weight, baby's older siblings, household smoking in the same room as the infant, and time of delivery before the third survey. Exclusive breastfeeding duration was classified into two categories (<4 and ≥ 4 months); partial breastfeeding duration into two (<6 and ≥ 6 months); maternal age into three (<29 , $29-31$, and $32+$ yr); 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); baby's birth weight into two (<2500 and $2500+$ g); number of baby's older siblings into two (0 and $1+$); and time of delivery before the third survey into three (16-19, 20, and 21-24 months). To lower the possibility of reverse causation, we also conducted analyses that were limited to 699 infants without suspected atopic eczema in the second survey. All computations were performed using

SAS SOFTWARE, version 9.1 (SAS Institute, Inc., Cary, NC, USA).

Results

Of the 763 mother–child pairs who participated in the third survey, 131 infants were still receiving breast milk at the time of the third survey. Only 10 infants had never been breastfed. By the third survey, 142 infants (18.6%) were revealed to have developed atopic eczema based on the ISAAC criteria.

Table 1 shows the distribution of selected characteristics among 763 parent–child pairs. About 30% of mothers were from 29 to 31 yr of age at baseline, and about 13% of mothers had smoked during pregnancy. A quarter of infants had been exposed to smoking in the household. Approximately half completed the third survey at 20 months postpartum.

Table 2 gives ORs and the 95% CIs for relationships between breastfeeding duration and the risk of atopic eczema. Compared with less than 4 months of exclusive breastfeeding, breastfeeding for 4 months or more was not statistically significantly associated with the risk of atopic eczema. In addition, crude OR for 6 months or more vs. less than 6 months of partial breastfeeding duration was not statistically significant. Adjustment for maternal age, maternal and paternal history of asthma, atopic eczema, and allergic rhinitis, indoor domestic pets, family income, maternal and paternal education, maternal smoking during pregnancy, baby's sex, baby's birth weight, baby's older siblings, household smoking in the same room as the infant, and time of delivery before the third survey did not appreciably change the results.

Table 3 presents analyses that excluded the 64 infants with suspected atopic eczema in the second survey. There was no material relationship between prolonged exclusive breastfeeding duration and the risk of atopic eczema in the multivariate model. However, partial breastfeeding for 6 months or more was marginally significantly associated with an increased risk of atopic eczema. After adjustment for confounders under study, the positive association was slightly evident although the adjusted ORs remained of borderline significance.

When classifying infants according to whether there was a negative or positive allergic history in at least one parent, in an overall analysis, no significant relationships were found between breastfeeding duration, regardless of exclusivity, and the risk of atopic eczema in infants with a negative or positive parental allergic history

Table 1. Distribution of selected characteristics of 763 parent–child pairs, OMCHS, Japan

Variable	No. (%)
Baseline characteristics	
Maternal age (yr)	
<29	278 (36.4)
29–31	228 (29.9)
≥32	257 (33.7)
Maternal history of asthma	80 (10.5)
Maternal history of atopic eczema	120 (15.7)
Maternal history of allergic rhinitis	256 (33.6)
Paternal history of asthma	64 (8.4)
Paternal history of atopic eczema	72 (9.4)
Paternal history of allergic rhinitis	143 (18.7)
Indoor domestic pets (cats, dogs, birds or hamsters)	93 (12.2)
Family income (yen/yr)*	
<4,000,000	211 (27.7)
4,000,000–5,999,999	313 (41.0)
≥6,000,000	239 (31.3)
Maternal education (yr)	
<13	212 (27.8)
13–14	329 (43.1)
≥15	222 (29.1)
Paternal education (yr)	
<13	289 (37.9)
13–14	127 (16.6)
≥15	347 (45.5)
Characteristics at postnatal assessment	
Maternal smoking during pregnancy	97 (12.7)
Baby's sex (male)	403 (52.8)
Baby's birth weight (g)	
<2500	44 (5.8)
≥2500	719 (94.2)
Baby's older siblings (one or more)	381 (49.9)
Household smoking in same room as infant	195 (25.6)
Time of delivery before third survey (months)	
16–19	263 (34.5)
20	370 (48.5)
21–24	130 (17.0)

*€1 = 160 yen.

Table 2. Odds ratios and 95% confidence intervals for atopic eczema in relation to breastfeeding duration in 763 infants, OMCHS, Japan

Breastfeeding duration	Risk (%)	Crude OR (95% CI)	Adjusted OR (95% CI)*
Exclusive breastfeeding			
<4 months	70/409 (17.1)	1.00	1.00
≥4 months	72/354 (20.3)	1.24 (0.86–1.78)	1.23 (0.84–1.81)
Partial breastfeeding			
<6 months	29/189 (15.3)	1.00	1.00
≥6 months	113/574 (19.7)	1.35 (0.88–2.14)	1.39 (0.88–2.26)

*Adjustment for maternal age, maternal and paternal history of asthma, atopic eczema, and allergic rhinitis, indoor domestic pets, family income, maternal and paternal education, maternal smoking during pregnancy, baby's sex, baby's birth weight, baby's older siblings, household smoking in same room as infant, and time of delivery before third survey.

(Table 4). After excluding 64 infants with suspected atopic eczema in the second survey, positive associations between breastfeeding duration and the risk of atopic eczema were statisti-

Table 3. Odds ratios and 95% confidence intervals for atopic eczema in relation to breastfeeding duration in 699 infants, with 64 infants with suspected atopic eczema in the second survey excluded, OMCHS, Japan

Breastfeeding duration	Risk (%)	Crude OR (95% CI)	Adjusted OR (95% CI)*
Exclusive breastfeeding			
<4 months	56/377 (14.9)	1.00	1.00
≥4 months	58/322 (18.0)	1.26 (0.84–1.88)	1.27 (0.83–1.95)
Partial breastfeeding			
<6 months	21/175 (12.0)	1.00	1.00
≥6 months	93/524 (17.8)	1.58 (0.97–2.69)	1.66 (0.99–2.92)

*Adjustment for maternal age, maternal and paternal history of asthma, atopic eczema, and allergic rhinitis, indoor domestic pets, family income, maternal and paternal education, maternal smoking during pregnancy, baby's sex, baby's birth weight, baby's older siblings, household smoking in same room as infant, and time of delivery before third survey.

Table 4. Odds ratios and 95% confidence intervals for atopic eczema in relation to breastfeeding duration in infants with a negative or positive parental allergic history, OMCHS, Japan

Breastfeeding duration	Adjusted OR (95% CI)*	
	Negative parental allergic history	Positive parental allergic history
Overall analysis (n = 763)	(n = 313)	(n = 450)
Exclusive breastfeeding		
<4 months	1.00	1.00
≥4 months	1.77 (0.90–3.55)	0.96 (0.59–1.55)
Partial breastfeeding		
<6 months	1.00	1.00
≥6 months	1.69 (0.74–4.29)	1.30 (0.74–2.35)
Analysis with suspected atopic eczema in the second survey excluded (n = 699)	(n = 287)	(n = 412)
Exclusive breastfeeding		
<4 months	1.00	1.00
≥4 months	2.41 (1.10–5.55)	0.84 (0.49–1.44)
Partial breastfeeding		
<6 months	1.00	1.00
≥6 months	3.39 (1.20–12.36)	1.33 (0.72–2.55)

*Adjustment for maternal age, indoor domestic pets, family income, maternal and paternal education, maternal smoking during pregnancy, baby's sex, baby's birth weight, baby's older siblings, household smoking in same room as infant, and time of delivery before third survey.

cally significant in infants without a parental allergic history: the multivariate ORs for 4 months or more of exclusive breastfeeding and 6 months or more of partial breastfeeding were 2.41 (95% CI, 1.10–5.55) and 3.39 (95% CI, 1.20–12.36), respectively. Neither exclusive nor partial breastfeeding duration was measurably related to the risk of atopic eczema in infants with a parental allergic history. No significant interactions were observed in the association of breastfeeding duration with the risk of atopic eczema between infants with a negative and

positive parental allergic history ($p = 0.22$ and 0.49 , and 0.07 and 0.14 , respectively, for homogeneity of OR for exclusive and partial breastfeeding duration in the overall analysis and the analysis that excluded suspected atopic eczema in the second survey).

Discussion

The current prospective study found no strong effects of either exclusive or partial breastfeeding on the risk of atopic eczema during the first 16–24 months of life. However, after excluding 64 infants identified with suspected atopic eczema in the second survey to limit reverse causation, exclusive breastfeeding for 4 months or more and partial breastfeeding for 6 months or more were independently associated with an increased risk of atopic eczema only among infants with no parent having a history of allergic disorders. The Danish National Birth Cohort found that exclusive breastfeeding for at least 4 months was significantly positively associated with the risk of atopic eczema in infants without a parental history of allergic diseases whereas there was no such relationship in infants with a parental allergic history (9). Another prospective study in Finland showed that, compared with children who had been fed a cow's milk-based formula during their first 2 wk, those who had been exclusively breastfed for at least 3 months had a significantly increased risk of atopic eczema at 4 yr of age in the subgroup with a negative, but not positive, parental history of atopy (10). Two Japanese cross-sectional studies found a significant positive association between breastfeeding and the prevalence of atopic eczema, especially among children without a parental allergic history (11, 12). These observations are partially consistent with the present results.

Strachan formulated the hygiene hypothesis, suggesting that early exposure to infections could reduce the risk of allergic disorders (15). A meta-analysis showed a protective association between breastfeeding and the risk of hospitalization for lower respiratory tract disease (16). Breastfeeding might alleviate the impact of immune stimulants such as bacteria and endotoxins. Thus, breastfeeding may be a risk factor for allergic disorders. However, further adjustment for the number of early infections occurring before 6 months of age did not change the positive relationship between exclusive breastfeeding and the risk of atopic eczema in children without a parental allergic history in the Danish National Birth Cohort (9). As information on early infections was not

available in the second survey of the OMCHS, we could not examine the hypothesis. Nevertheless, this hypothesis is not likely to explain the lack of an association between breastfeeding and the risk of atopic eczema in infants with a parental allergic history in the present study.

The observed positive association between breastfeeding and atopic eczema in the current study might be caused by unrecognized active substances in breast milk. Dioxins and polychlorinated biphenyls (PCBs) are lipophilic compounds and are present in human milk. A study in the Netherlands showed that plasma PCB levels were 3.6 times higher in breast-fed infants than in their formula-fed peers and that the breastfeeding period and breast milk PCB levels were significantly positively related to plasma PCB levels in the breast-fed group (17). In Taiwanese infants at 12 months of age, by calculating toxic equivalency quotient (TEQ) values according to the World Health Organization (WHO), average daily intake of polychlorinated dibenzo-*p*-dioxins and polychlorinated dibenzofurans was estimated to be 2.1 pg WHO-TEQ/kg/day for formula-fed infants and 13 pg WHO-TEQ/kg/day for breast-fed infants (18). Weisglas-Kuperus et al. found that perinatal exposure to PCBs and dioxins was associated with changes in the T-cell lymphocyte population although PCB exposure was not related to the prevalence of eczema in healthy Dutch preschool children (19). A laboratory study demonstrated that 2,3,7,8-tetrachlorodibenzo-*p*-dioxin enhanced spontaneous immunoglobulin E production in B cells from Japanese atopic patients (20). In Japan, the intake of fish is high. Methylmercury and dioxins are accumulated in fish and shellfish through the marine food web. Such substances might have been transferred from mothers to their infants through breast milk as well as during pregnancy.

The current study had some methodological strengths. Study subjects were homogeneous with regard to having the same residential background. We took into consideration comprehensive information on potential confounding factors. The definition of atopic eczema was based on the ISAAC questions although validation tests of the ISAAC questions have not been performed for Japanese infants. No attempt was made to ascertain outcome status through reviews of medical records. In addition, the definition of suspected atopic eczema in our second survey might have been crude. Of 64 infants identified with suspected atopic eczema in the second survey, 36 infants (56.3%) were classified as having atopic eczema

based on the ISAAC questions in the third survey. The prospective design and the relatively short time of delivery before the third survey were not likely to increase recall bias associated with the feeding pattern after birth. However, the Melbourne Atopy Cohort Study found that early signs of atopic disease were independently associated with *c.* 30% reduction in the risk of ceasing exclusive breastfeeding (21). Because of public awareness of the health-promoting effects of breastfeeding, mothers of infants with onset of atopic eczema during the breastfeeding period might have continued breastfeeding. The possible influence of reverse causation should be taken into careful consideration. Survival analysis can assess only an effect of breastfeeding before the development of atopic eczema. However, information on the exact onset of atopic eczema was not available in the present study. The exclusion of 64 infants with suspected atopic eczema revealed by the second survey could minimize the possibility of reverse causation although the excluded children might differ in several characteristics such as etiology and severity. However, we could not avoid overlap between exposure and disease outcome because breastfeeding duration was assessed in the third survey when the outcome was known. In addition, mothers who breastfed longer were likely to be aware of their child's skin problems. The consequence could bias the estimates of the association in a positive direction.

Other limitations of the present study should be discussed. The follow-up rate was not good. Of the 1002 participants at baseline, 239 mother-child pairs did not take part in the third survey. There were no material differences between the 239 non-participants and the 763 participants in the third survey with regard to distribution of maternal age, maternal and paternal history of asthma, atopic eczema, and allergic rhinitis, and indoor domestic pets (data not shown). Compared with non-participants in the third survey, participants were less likely to report low family income and low maternal and paternal educational level. Moreover, at baseline, the participation rate in Neyagawa City was low (17.2%) and that in other areas could not be calculated. The infants in the current study were not a representative sample of Japanese infants in the general population and the present findings may not be generalized. Educational levels in the present study population were higher 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 (22). The corresponding figures for the current study were 27.8%, 43.1%, 29.1%, and 0.0%, respectively. The lifetime prevalence of atopic eczema might be higher among parents in this analysis than among the general population. The lifetime prevalence of atopic eczema was reported to be 4.2% and 4.4%, respectively, for Japanese men and women aged 30–39 yr according to UK Working Party's diagnostic criteria (23). On the contrary, the prevalence of atopic eczema might be lower among infants reported here than among the general population. For example, a report from Japan showed that eczema was observed in 32% of the 10-month-old infants and 20% of the 3-yr-old children who came to public health examinations (24). Breast-feeding duration in our study population may be longer than in the general population. In the present study population, 75.2% of mothers had breastfed their infants for 6 months or more, whereas only 39.2% of mothers had performed so for 7 months or more in Okinawa, Japan (11). The present study did not have substantial statistical power although significant positive associations were detected.

This is the first prospective study on the relationship between breastfeeding and the risk of atopic eczema in Japan. Overall, neither exclusive nor partial breastfeeding had a strong impact on the risk of atopic eczema, although a parental allergic history may affect the risk. Further investigations of the effects of breastfeeding on atopic eczema in Japan as well as in other localities are required.

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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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