

Breastfeeding and the risk of wheeze and asthma in Japanese infants: The Osaka Maternal and Child Health Study

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Epidemiological evidence for an effect of breastfeeding on asthma continues to be inconclusive. The present prospective study examined the relationship between breastfeeding and the risk of wheeze and asthma in Japanese infants. 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. Data on breastfeeding, wheeze, and asthma were obtained from questionnaires in the third survey from 16 to 24 months postpartum. Adjustment was made for 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 older siblings, household smoking in the same room as the infant, and time of delivery before the third survey. By the third survey, the cumulative incidence of wheeze and asthma was 22.1% and 4.3%, respectively. Neither exclusive breastfeeding for 4 months or more nor partial breastfeeding for 6 months or more were materially related to the risk of wheeze. No measurable association was observed between exclusive breastfeeding for 4 months or more and the risk of asthma. Partial breastfeeding for 6 months or more was inversely related to the risk of asthma although the adjusted odds ratio (OR) was not statistically significant. When infants were stratified according to whether there was a negative or positive allergic history in at least 1 parent, a nearly 40% and 60% decrease, respectively, in the ORs were found for exclusive and partial breastfeeding only in infants without a parental allergic history, although the ORs were not statistically significant. The present prospective study showed no statistically significant relationship between breastfeeding duration and the risk of wheeze or asthma in Japanese infants.

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Epidemiological evidence for an effect of breastfeeding on asthma continues to be inconclusive (1–16). A prospective birth cohort study in Sweden found that longer breastfeeding duration reduced the risk of asthma during the first 4 yr of life, especially among infants without heredity for allergy (1). Exclusive breastfeeding for at

least 4 months after birth significantly reduced the risk of asthma at age 6 yr in an Australian cohort study (2). No association was observed between breastfeeding and the risk of asthma in two cohort studies in Australia and the United Kingdom (3, 4). On the other hand, breastfeeding for 4 months or longer was associated with an

increased risk of asthma at 9–26 yr in a New Zealand birth cohort (5). The Tucson Children's Respiratory Study found that exclusive breastfeeding for 4 months or more was related to an increased risk of asthma and recurrent wheeze beginning at the age of 6 yr although an association with recurrent wheeze early in life was preventive (6). However, a systematic review with meta-analysis of prospective studies showed a significant protective association between breastfeeding and the risk of asthma (17).

With respect to epidemiological information in Japan, a population-based case-control study among schoolchildren showed that breastfeeding was significantly positively associated with the prevalence of asthma (7). In two cross-sectional studies, breastfeeding was related to a higher prevalence of atopic eczema, but not wheeze, among schoolchildren (8, 9). Because there has been no prospective study of the relationships between breastfeeding and the risk of asthma and wheeze in Japan, the present study examined those relationships among infants using data from 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. 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 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 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. Also, 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, 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 for final analysis included information on 763 mother-child pairs. The ethics committee of the Osaka City University School of Medicine approved the OMCHS.

Measurements

In the baseline survey, each participant filled out a set of two self-administered questionnaires. Also, a self-administered questionnaire was 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.

At baseline, a questionnaire asked 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 present study.

A self-administered questionnaire in the second survey elicited information on maternal smoking during pregnancy, baby's sex, date of birth of the infant born after the baseline survey, number of baby's older siblings, and smoking in the household after birth. 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, asthma status, and symptoms of wheeze 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. The definition of asthma used in this study was determined by a positive response to the written question 'Has your child been diagnosed by a physician as having asthma?' Wheeze was defined as present if the mother answered 'yes' to the written question 'Has your child had wheezing or whistling in the chest in the last 12 months?'

Statistical analysis

Logistic regression analysis was used to compare the risk of asthma and wheeze according to breastfeeding duration. Multiple logistic regression analysis was used to control for the potential confounding factors under study. 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 older siblings, household smoking in the same room as the infant, and time of delivery before the third survey were selected *a priori* as potential confounders. 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); 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). All computations were performed using SAS software, version 9.1 (SAS Institute Inc., Cary, NC, USA).

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

Variable	n (%)
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 older siblings (1 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.

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, the cumulative incidence of wheeze and asthma was 22.1% and 4.3%, respectively.

Table 1 gives the distribution of selected characteristics among 763 parent–child pairs. About 30% of mothers were from 29 to 31 yr of age at baseline. Many more parents had a history of allergic rhinitis than a history of asthma and atopic eczema. About 13% of mothers had smoked during pregnancy. A quarter of infants had been exposed to household smoking. The proportions of mother–child pairs taking part in the third survey at 16–19, 20, and 21–24 months postpartum were 34.5%, 48.5%, and 17.0%, respectively.

Table 2 provides odds ratios (ORs) and 95% confidence intervals for wheeze and asthma

Table 2. Odds ratios and 95% CIs for wheeze and asthma according to breastfeeding duration in 763 infants, OMCHS, Japan

Breastfeeding duration	Risk (%)	Crude OR (95% CI)	Adjusted OR (95% CI)*
Wheeze			
Exclusive breastfeeding			
<4 months	88/409 (21.5)	1.00	1.00
≥4 months	81/354 (22.9)	1.08 (0.77–1.52)	1.05 (0.73–1.50)
Partial breastfeeding			
<6 months	39/189 (20.6)	1.00	1.00
≥6 months	130/574 (22.7)	1.13 (0.76–1.70)	1.19 (0.78–1.84)
Asthma			
Exclusive breastfeeding			
<4 months	17/409 (4.2)	1.00	1.00
≥4 months	16/354 (4.5)	1.09 (0.54–2.20)	1.07 (0.52–2.23)
Partial breastfeeding			
<6 months	12/189 (6.4)	1.00	1.00
≥6 months	21/574 (3.7)	0.56 (0.27–1.20)	0.63 (0.29–1.40)

*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 older siblings, household smoking in same room as infant, and time of delivery before third survey. CI, confidence interval.

according to breastfeeding duration. Crude OR of the risk of wheeze for comparison of 4 months or more with less than 4 months of exclusive breastfeeding duration was not statistically significant. Compared with less than 6 months of partial breastfeeding, 6 months or more of partial breastfeeding was not statistically significantly related to the risk of wheeze. 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 older siblings, household smoking in the same room as the infant, and time of delivery before the third survey did not materially alter the results. Exclusive breastfeeding for 4 months or more was not independently associated with the risk of asthma in the multivariate model. Partial breastfeeding for 6 months or more was inversely related to the risk of asthma although the adjusted OR was not statistically significant.

When infants were stratified according to whether there was a negative or positive allergic history in at least one parent, there was a nearly 40% and 60% decrease in the OR, respectively, for exclusive and partial breastfeeding only in infants without a parental allergic history although the ORs were not statistically significant (Table 3). Neither exclusive nor partial breastfeeding duration was evidently associated with the risk of wheeze in infants without a parental allergic history as well as in those with a parental allergic history. No material differences

Table 3. Odds ratios and 95% CIs for wheeze and asthma according to breastfeeding duration in 763 infants with a negative or positive parental allergic history, OMCHS, Japan

Breastfeeding duration	Adjusted OR (95% CI)*	
	Negative parental allergic history (n = 313)	Positive parental allergic history (n = 450)
Wheeze		
Exclusive breastfeeding		
<4 months	1.00	1.00
≥4 months	0.79 (0.43–1.44)	1.03 (0.65–1.63)
Partial breastfeeding		
<6 months	1.00	1.00
≥6 months	0.91 (0.45–1.91)	1.20 (0.71–2.08)
Asthma		
Exclusive breastfeeding		
<4 months	1.00	1.00
≥4 months	0.62 (0.17–2.05)	1.34 (0.52–3.54)
Partial breastfeeding		
<6 months	1.00	1.00
≥6 months	0.38 (0.11–1.37)	0.80 (0.30–2.39)

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

were observed in the risk of wheeze or asthma in relation to breastfeeding duration between infants with a negative and positive parental allergic history ($p = 0.72, 0.95, 0.24$, and 0.40 for homogeneity of OR for exclusive and partial breastfeeding duration, respectively).

Discussion

The present prospective study showed no statistically significant relationship between breastfeeding duration and the risk of wheeze or asthma in Japanese infants. An Australian cohort study demonstrated that stopping breastfeeding before 8 months was associated with an increased risk of wheezing and lower respiratory illness in the first year of life (18). In a German cohort study, both exclusive breastfeeding for 3 months or more and partial breastfeeding for 6 months or more were significantly inversely related to the risk of asthma at 2 yr (10). Exclusive breastfeeding for 4 months or more and partial breastfeeding for 6 months or more were associated with a decreased risk of wheeze and asthma up to 2 yr of age in a Swedish prospective study (11). A cross-sectional study in Canada showed a significant inverse relationship between breastfeeding for 9 months or more and the prevalence of wheeze and asthma in children aged 12–23 months (12). The Third National Health and Nutrition Examination Survey found an inverse association of ever having been breast-

fed with the prevalence of recurrent wheeze and asthma in children less than 24 months of age although associations with partial and exclusive breastfeeding for 4 months or more were not statistically significant (14). Our results are generally at variance with these findings.

Several components of human milk may influence the allergic status of the infant. Oddy et al. observed that infants with both a longer duration of breastfeeding and fed maternal milk with a medium-high concentration of transforming growth factor (TGF)- β 1 had reduced risk of wheeze in the first year of life although concentrations of interleukin-10 (IL-10), tumor necrosis factor (TNF)- α , and soluble form of CD14 in human milk were not related to wheeze (19). Compared with partial or no breastfeeding, exclusive breastfeeding at 1 month of age was associated with a 35% increase in whole blood Th₁ cytokine levels, but not Th₂ or CD4 levels, in US children at 24 months of age (20). Böttcher et al. found no association between the levels of the cytokines or chemokines nor secretory-immunoglobulin A (IgA) in breast milk and either development of allergic symptoms or salivary IgA levels during the first 2 yr of life, however (21). On the other hand, as a consequence of recent changes in the environment in developed countries, mothers may transfer elevated levels of allergens, pollutants, and environmental chemicals to their infants through breast milk as well as during pregnancy (22). A study in the Netherlands showed that plasma polychlorinated biphenyl levels were 3.6 times higher in breast-fed infants than in their formula-fed peers and that the breastfeeding period and breast milk polychlorinated biphenyl levels were significantly positively related to plasma polychlorinated biphenyl levels in the breast-fed group (23). The lack of a relationship between breastfeeding duration and the risk of wheeze and asthma in the current study may be ascribed to unknown active agents in breast milk that obscure any beneficial effect of breastfeeding. Alternatively, our findings may simply be a chance phenomenon.

The Avon Longitudinal Study of Parents and Children found that severe respiratory syncytial virus (RSV) bronchiolitis in infancy was significantly associated with an increased risk of subsequent wheeze and asthma (24). In a case-control study among Alaskan infants, breastfeeding was significantly related to a decreased risk of RSV infection resulting in hospitalization (25). A meta-analysis of seven cohort studies showed a significant inverse relationship between breastfeeding and hospitalization for lower respiratory tract disease (26). However, a review concluded

that lack of breastfeeding did not appear to increase the risk of severe RSV lower respiratory tract infections (27). On the other hand, a recent preliminary report observed that milk from mothers of infants hospitalized with bronchiolitis had significantly greater numbers of viable cells compared with milk obtained from mothers of healthy infants and that cells from milk of mothers of bronchiolitic, but not healthy, infants produced higher levels of IL-10 and reduced levels of interferon (INF)- γ *ex vivo* in response to stimulation by live RSV, demonstrating a Th₂ bias (28).

The present study had some methodological strengths. Study subjects were homogeneous in terms of having the same residential background. Extensive information on potential confounding factors was controlled for in data analysis. The prospective design and the relatively short time of delivery before the third survey were not likely to cause recall bias in relation to the feeding pattern after birth. However, regarding the possibility of reverse causation, mothers of infants with onset of wheeze or asthma during the breastfeeding period might have continued breastfeeding.

There are other weaknesses in the present study. 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 a low maternal and paternal educational level. Furthermore, at baseline, the participation rate in Neyagawa City was low (17.2%) and that in other areas could not be calculated. Because data on personal characteristics among non-participants in the baseline survey were not available, we could not assess the differences between participants and non-participants at baseline. 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 (29). The corresponding figures for the current study were 27.8%, 43.1%, 29.1%, and 0.0%, respectively. Therefore, the infants in this study were an unrepresentative sample of Japanese infants in the general population and the present findings may not be generalized. If the current study had had substantial statistical power, inverse relationships between

breastfeeding duration and the risk of asthma may have been statistically significant.

Our prospective study found no material associations between breastfeeding and the risk of wheeze or asthma in Japanese infants. Larger studies are needed to draw a conclusion as to the question of whether breastfeeding confers protection against wheeze and asthma in Japan. Further investigations of other populations, especially in Asia, are also required to assess the effects of breastfeeding on asthma.

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Appendix

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