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## Breastfeeding duration is inversely associated with asthma in Japanese children aged 3 years

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### ABSTRACT

**Objective:** Recent meta-analyses found an inverse relationship between breastfeeding duration and asthma in children. The present cross-sectional study investigated the associations between breastfeeding duration and the prevalence of wheeze and asthma in Japanese children aged 3 years. **Methods:** Subjects were 6412 children who participated in the Kyushu Okinawa Child Health Study. Data were collected using a self-administered questionnaire. Wheeze was defined according to the criteria of the International Study of Asthma and Allergies in Childhood. Asthma was considered present if the child had been diagnosed by a physician as having asthma. Associations of breastfeeding duration with wheeze and asthma were estimated using multivariate generalized estimating equation methods adjusted for maternal, family, and health characteristics. **Results:** The prevalence values of wheeze and asthma were 19.5% and 7.0%, respectively. Compared with <4 months of exclusive breastfeeding, exclusive breastfeeding for ≥4 months was not significantly associated with wheeze or asthma. Compared with <10 months of breastfeeding duration regardless of exclusivity, 10 to <14 months, 14 to <19 months, and 19 months or more of breastfeeding duration regardless of exclusivity were independently inversely related to asthma: the adjusted odds ratios [ORs; 95% confidence intervals (CIs)] were 0.69 (0.52–0.91,  $p = 0.01$ ), 0.73 (0.56–0.97,  $p = 0.03$ ), and 0.67 (0.51–0.88,  $p = 0.004$ ), respectively. No association was found between breastfeeding duration regardless of exclusivity and wheeze. **Conclusions:** We confirmed an inverse association between breastfeeding duration regardless of exclusivity and asthma.

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Asthma; breastfeeding; children; cross-sectional study; Japan

## Introduction

Breast milk is the first food consumed by most newborns. Human breast milk contains not only nutrients necessary for infant growth and development but also numerous bioactive substances [1]. It is well established that breastfeeding is associated with a decreased risk of various disorders such as acute otitis media, severe lower respiratory tract infections, and atopic dermatitis [2]. A systematic review found that most studies demonstrated an association of breastfeeding with improved lung function [3], which might reduce the risk of developing asthma.

In 2014, a meta-analysis including 113 studies showed that children who are breastfed longer have a significantly reduced risk of asthma and that this risk reduction is most pronounced in children aged 0–2 years and decreases with age, but is still significant in children aged 7 years or older [4]. Another meta-analysis in 2015 based on 29 studies

found a significantly lower risk of asthma at 5–18 years with longer vs. shorter breastfeeding duration, although no significant association was observed between exclusive breastfeeding for longer than 3–4 months and asthma at 5–18 years in a sub-analysis based on eight studies [5]. Most of the epidemiological investigations included in the above-mentioned meta-analyses were performed in Western countries, but a significant inverse association was shown between longer breastfeeding duration and asthma in both Western and non-Western countries in a meta-analysis in 2014. In Japan, epidemiological evidence on this issue has been limited and inconsistent [6–12].

These conflicting results highlight the need for more studies on the association between breastfeeding and asthma in Japan. To accumulate further evidence, we conducted a cross-sectional study of the association between breastfeeding and the prevalence of wheeze and

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asthma in Japanese children aged 3 years using data from the Kyushu Okinawa Child Health Study (KOCHS).

## Methods

### Subjects

In Japan, when children reach the age of 3, their municipality of residence provides them with a physical examination under the Maternal and Child Health Law. Eligible study subjects were 68,527 children aged 3 years who lived in one of 45 municipalities; there were 32 municipalities in Fukuoka Prefecture including the metropolitan area of Fukuoka, six municipalities in five prefectures other than Fukuoka Prefecture on Kyushu island in southern Japan, and seven municipalities in Okinawa Prefecture, an island chain in the southwest of Japan. Each eligible subject received his or her physical examination at a public health center in his or her municipality of residence between May 2012 and March 2014. During the physical examination, a 38-page self-administered questionnaire with a postage-paid, addressed return envelope was offered to the parents or guardians of all 68,527 eligible children; the parents or guardians of 62,449 children took the materials home with them. In the case of twins, only the older child was enrolled in our study. A total of 6576 parents or guardians gave their written informed consent and mailed the completed questionnaire to the data management center (participation rate = 9.6%). Our research technicians completed missing answers and/or illogical data by telephone interview with individual parents or guardians. Excluded from the present analysis were 164 children with missing data on the variables under study. Thus, the final sample consisted of 6412 children (9.4% of the 68,527 eligible children). The KOCHS was approved by the ethics committees of the Faculty of Medicine, Fukuoka University, and Ehime University Graduate School of Medicine.

### Measurements

The self-administered questionnaire included questions regarding wheeze and asthma. According to the International Study of Asthma and Allergies in Childhood (ISAAC) [13], wheeze was defined as present if the parent or guardian answered “yes” to the question “Has your child had wheezing or whistling in the chest in the last 12 months?” Asthma was considered present if the child had been diagnosed by a physician as having asthma at any time since birth. The questionnaire also asked about maternal age at birth, date of birth, sex, region of residence, number of siblings, maternal smoking during pregnancy, household smoking during the first year of

life, paternal and maternal educational levels, household income, paternal and maternal history of asthma, atopic eczema, and allergic rhinitis, 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 [7–10]. 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.

### Statistical analysis

Exclusive breastfeeding duration was classified into two categories with the cutoff point set at the month nearest to the median (<4 and ≥4 months), and breastfeeding duration regardless of exclusivity was classified into four at the nearest quartile points (<10, 10 to <14, 15 to <19, and ≥19 months) [14]. Based on a review of the literature, maternal age at birth, age, sex, number of siblings, maternal smoking during pregnancy, household smoking during the first year of life, paternal and maternal educational levels, household income, and paternal and maternal history of asthma, atopic eczema, and allergic rhinitis were selected as *a priori* potential confounding factors. Logistic regression analysis was used to estimate crude odds ratios (ORs) and 95% confidence intervals (CIs) for wheeze and asthma in relation to breastfeeding duration. Multiple generalized estimating equation methods with logit link were used to account for clustering within municipalities via the PROC GENMOD procedure. Multiplicative interactions between breastfeeding and parental allergic history were tested using a likelihood ratio test. All statistical analyses were performed using the SAS software package version 9.4 (SAS Institute, Inc., Cary, NC, USA).

## Results

The prevalence values of wheeze and asthma were 19.5% and 7.0%, respectively, among the 6412 children. Approximately 74% of the subjects had one or more siblings (Table 1). About 9% and 25% had been exposed to maternal smoking during pregnancy and household smoking during the first year of life, respectively. Only 1.9% (*n* = 120) of the children were not breastfed at all or were breastfed for less than 1 month.

Table 2 gives ORs and 95% CIs for wheeze and asthma in relation to breastfeeding duration. Compared with <4 months of exclusive breastfeeding, exclusive breastfeeding for ≥4 months was not significantly associated with the prevalence of wheeze or asthma. After adjustment for the confounding factors under study, we

**Table 1.** Distribution of selected characteristics in 6412 children aged 3 years.

| Variable                                        | n (%) or mean $\pm$ SD |
|-------------------------------------------------|------------------------|
| Maternal age at birth, years, mean $\pm$ SD     | 31.1 $\pm$ 4.7         |
| Age, months, mean $\pm$ SD                      | 38.7 $\pm$ 6.8         |
| Male sex                                        | 3258 (50.8)            |
| Number of siblings                              |                        |
| 0                                               | 1698 (26.5)            |
| 1                                               | 3334 (52.0)            |
| $\geq 2$                                        | 1380 (21.5)            |
| Maternal smoking during pregnancy               | 602 (9.4)              |
| Household smoking during the first year of life | 1611 (25.1)            |
| Paternal educational level, years               |                        |
| <13                                             | 1976 (30.8)            |
| 13–14                                           | 933 (14.6)             |
| $\geq 15$                                       | 3503 (54.6)            |
| Maternal educational level, years               |                        |
| <13                                             | 1527 (23.8)            |
| 13–14                                           | 2147 (33.5)            |
| $\geq 15$                                       | 2738 (42.7)            |
| Household income, yen/year                      |                        |
| <4,000,000                                      | 1991 (31.1)            |
| 4,000,000–5,999,999                             | 2183 (34.1)            |
| $\geq 6,000,000$                                | 2238 (34.9)            |
| Paternal history of asthma                      | 765 (11.9)             |
| Paternal history of atopic eczema               | 646 (10.1)             |
| Paternal history of allergic rhinitis           | 2312 (36.1)            |
| Maternal history of asthma                      | 866 (13.5)             |
| Maternal history of atopic eczema               | 1073 (16.7)            |
| Maternal history of allergic rhinitis           | 2596 (40.5)            |

SD, standard deviation.

observed no association between exclusive breastfeeding for <4 months and the prevalence of wheeze or asthma when compared with exclusive breastfeeding for  $\geq 4$  months. Compared with <10 months of breastfeeding duration regardless of exclusivity, 10 to <14 months, 14 to <19 months, and 19 months or more of breastfeeding duration regardless of exclusivity were significantly related to a lower prevalence of asthma. After adjustment for confounding factors, the inverse association was slightly attenuated but remained statistically significant: the adjusted ORs (95% CIs) for 10 to <14 months, 14 to <19 months, and 19 months or more of breastfeeding duration regardless of exclusivity were 0.69 (0.52–0.91,  $p = 0.01$ ), 0.73 (0.56–0.97,  $p = 0.03$ ), and 0.67 (0.51–0.88,  $p = 0.004$ ), respectively. No such inverse relationship was observed between breastfeeding duration regardless

of exclusivity and the prevalence of wheeze in the multivariate model.

Out of the 446 children classified as having asthma, we conducted a sensitivity analysis assessing the 236 children who were classified as having current asthma, i.e., those for whom the parents or guardians reported current medical treatment for asthma at the time of the survey. For the current asthma patients, a significant inverse association was observed only between 19 months or more breastfeeding duration regardless of exclusivity and the prevalence of current asthma: the adjusted ORs (95% CIs) for 10 to <14 months, 14 to <19 months, and 19 months or more of breastfeeding duration regardless of exclusivity were 0.75 (0.52–1.09,  $p = 0.14$ ), 0.75 (0.51–1.08,  $p = 0.12$ ), and 0.62 (0.43–0.91,  $p = 0.01$ ), respectively.

When breastfeeding duration regardless of exclusivity was classified into two categories (<10 and  $\geq 10$  months), the adjusted OR (95% CI) for asthma associated with 10 months or more of breastfeeding duration regardless of exclusivity was 0.70 (0.56–0.87,  $p = 0.002$ ). When children were divided according to whether there was a positive ( $n = 4516$ ) or negative ( $n = 1896$ ) allergic history in at least one parent (Table 3), an independent inverse association was found between 10 months or more of breastfeeding duration regardless of exclusivity and asthma only in children with a parental allergic history: the adjusted OR (95% CI) was 0.68 (0.53–0.87,  $p = 0.002$ ). The corresponding figure for children without a parental allergic history was 0.84 (0.49–1.46,  $p = 0.54$ ); however, the multiplicative interaction between breastfeeding duration regardless of exclusivity and parental allergic history affecting asthma was not significant ( $p$  for interaction = 0.50).

## Discussion

The current results are generally in agreement with those of meta-analyses in 2014 [4] and 2015 [5] that showed protective effects of breastfeeding against the risk of asthma. In the Generation R Study in the Netherlands,

**Table 2.** ORs and 95% CIs for wheeze and asthma in relation to breastfeeding duration in 6412 Japanese children aged 3 years.

|                                                          | Wheeze          |                   |                                   |                | Asthma         |                   |                                   |                |
|----------------------------------------------------------|-----------------|-------------------|-----------------------------------|----------------|----------------|-------------------|-----------------------------------|----------------|
|                                                          | Prevalence (%)  | Crude OR (95% CI) | Adjusted OR (95% CI) <sup>a</sup> | <i>p</i> value | Prevalence (%) | Crude OR (95% CI) | Adjusted OR (95% CI) <sup>a</sup> | <i>p</i> value |
| Exclusive breastfeeding duration, months                 |                 |                   |                                   |                |                |                   |                                   |                |
| <4                                                       | 590/3127 (18.9) | 1.00              | 1.00                              |                | 203/3127 (6.5) | 1.00              | 1.00                              |                |
| $\geq 4$                                                 | 658/3285 (20.0) | 1.08 (0.95–1.22)  | 1.09 (0.96–1.24)                  | 0.18           | 243/3285 (7.4) | 1.15 (0.95–1.40)  | 1.12 (0.92–1.37)                  | 0.26           |
| Breastfeeding duration regardless of exclusivity, months |                 |                   |                                   |                |                |                   |                                   |                |
| <10                                                      | 282/1390 (20.3) | 1.00              | 1.00                              |                | 127/1390 (9.1) | 1.00              | 1.00                              |                |
| 10 to <14                                                | 296/1597 (18.5) | 0.89 (0.75–1.07)  | 0.93 (0.77–1.12)                  | 0.44           | 100/1597 (6.3) | 0.66 (0.51–0.87)  | 0.69 (0.52–0.91)                  | 0.01           |
| 14 to <19                                                | 335/1688 (19.9) | 0.97 (0.82–1.16)  | 1.01 (0.84–1.22)                  | 0.89           | 111/1688 (6.6) | 0.70 (0.54–0.91)  | 0.73 (0.56–0.97)                  | 0.03           |
| $\geq 19$                                                | 335/1737 (19.3) | 0.94 (0.79–1.12)  | 0.93 (0.78–1.12)                  | 0.46           | 108/1737 (6.2) | 0.66 (0.50–0.86)  | 0.67 (0.51–0.88)                  | 0.004          |

<sup>a</sup> Adjustment for maternal age at birth, age, sex, number of siblings, maternal smoking during pregnancy, household smoking during the first year of life, paternal and maternal educational levels, household income, and paternal and maternal history of asthma, atopic eczema, and allergic rhinitis. OR, odds ratio; CI, confidence interval.

**Table 3.** Adjusted ORs and 95% CIs for wheeze and asthma in relation to breastfeeding duration in 6412 Japanese children with positive or negative parental allergic history.

| Breastfeeding duration regardless of exclusivity, months | Adjusted OR (95% CI) <sup>a</sup>             |                                               | <i>p</i> for interaction |
|----------------------------------------------------------|-----------------------------------------------|-----------------------------------------------|--------------------------|
|                                                          | Negative parental allergic history (n = 1896) | Positive parental allergic history (n = 4516) |                          |
| Wheeze                                                   |                                               |                                               |                          |
| <10                                                      | 1.00                                          | 1.00                                          |                          |
| ≥10                                                      | 0.84 (0.62–1.15)                              | 1.00 (0.84–1.20)                              | 0.40                     |
| Asthma                                                   |                                               |                                               |                          |
| <10                                                      | 1.00                                          | 1.00                                          |                          |
| ≥10                                                      | 0.84 (0.49–1.46)                              | 0.68 (0.53–0.87)                              | 0.50                     |

<sup>a</sup>Adjustment for maternal age at birth, age, sex, number of siblings, maternal smoking during pregnancy, household smoking during the first year of life, paternal and maternal educational levels, and household income.  
OR, odds ratio; CI, confidence interval.

compared with 0.1 to <2 months of breastfeeding duration regardless of exclusivity, breastfeeding regardless of exclusivity for ≥6 months was significantly associated with a reduced risk of current asthma at age 6 years [15]. In another birth cohort study in the Netherlands, children breastfed regardless of exclusivity for >16 weeks had a significantly lower asthma risk at 3–8 years of age [16]. In a birth cohort study in New Zealand, longer durations of both exclusive and any breastfeeding significantly reduced the risk of doctor-diagnosed asthma [17]. Our results are consistent with these observations, but are at variance with those of a German birth cohort study that found no association between breastfeeding for at least 6 months and asthma incidence up to age 20 years [18]. Our finding of the absence of an association between exclusive breastfeeding and asthma is in accordance with some previous studies [19, 20]. A birth cohort study in Hong Kong showed no association of exclusive breastfeeding for 3 months or more, compared with never breastfeeding, with hospitalization for asthma to 12 years [19]. No association was found between exclusive breastfeeding duration and asthma at age 7 years in a birth cohort study of Danish children born to mothers with a history of asthma [20].

Our results regarding wheeze are in agreement with those of another recent study that found no association between breastfeeding and the risk of wheeze [20]. On the other hand, some previous studies have shown an inverse association between breastfeeding and wheeze [15, 17, 21, 22]. Breastfeeding regardless of exclusivity for 3 months or more was significantly inversely related to persistent, but not transient early, intermediate onset, or late onset, wheeze until the age of 8 years [21]. In a birth cohort study in New Zealand, longer durations of both exclusive and any breastfeeding significantly reduced the risk of wheeze at 15 months of age [17]. These are at variance with our findings.

In a previous cohort study in Japan, neither exclusive nor partial breastfeeding was related to the risk of wheeze or asthma in Japanese infants [9]. A Japanese nationwide birth cohort study found that, compared with formula feeding only, exclusive breastfeeding at 6–7 months of age was not associated with hospitalization for asthma between the ages of 6 and 42 months, although an additional month of breastfeeding was significantly associated with a decreased risk of hospitalization for asthma [12]. These findings are in partial accordance with our results.

It should be noted that the various studies mentioned here have used a variety of outcome definitions, study designs and populations, definitions of exposure to breastfeeding, and confounders, which makes it difficult to compare between studies.

Numerous bioactive substances contained in human breast milk produce a cascade of effects that contribute to the orchestration, development, and functions of the early immune system through a variety of mechanisms, including direct or indirect antimicrobial activity, modulating immune function, anti-inflammatory effects, and enhancing growth and development of the infant's tissues [1]. A systematic review demonstrated that breastfeeding is beneficial for lung function, with the most consistent effect being on increased forced vital capacity [3].

One methodological strength of the present study is the homogeneity of the study subjects with respect to their living in Kyushu Island and Okinawa Prefecture in Japan and their being 3 years old. Several limitations of the present study warrant mention. The cross-sectional nature of the study does not permit the assessment of causality owing to the uncertain temporality of the association. Infants at high risk for allergic diseases such as those with family history of allergic diseases or early signs of allergic diseases might be breastfed longer in an attempt to counteract this risk. We cannot exclude the possibility of reverse causation. When patients were stratified by parental allergic history, however, an inverse association between breastfeeding and asthma was observed only in children with a positive parental allergic history.

The participation rate was only 9.2% in the present study. In our previous cross-sectional study, the 2006 Fukuoka Child Health Study (FCHS), which used the same recruitment methods as the present study, the response rate was about 25% [10]. In the FCHS, we used a 20-page questionnaire. The low response rate in the present study might be attributed to the large size of our questionnaire (38 pages). In addition, epidemiological studies are not very common in Japan. Therefore, people are not very familiar with epidemiological studies and are unlikely to be interested in them. Subjects in the current

study were an unrepresentative sample of Japanese children in the general population, and the present findings may not be generalized. In fact, in this study, education levels were higher in the subjects' parents than in the general population [23].

The definitions of wheeze and asthma were based on self-reported responses, which allows for the possibility of recall bias. Regarding wheeze, we used questions from the ISAAC, though validation tests of these questions have not been performed for Japanese children aged 3 years. No attempt was made to ascertain outcome status through reviews of medical records. Data on IgE levels were not available in the present study because blood samples were not collected in the KOCHS. This may have influenced our results by attenuating the association because of non-differential outcome misclassification. However, the prevalence values of outcomes in the present study were similar to those in the FCHS: the prevalence values of wheeze and asthma based on the ISAAC criteria in the FCHS were 22.1% and 8.9%, respectively [10]. Breastfeeding duration was assessed 3 years after the birth of the children, and this delay allowed for the possibility of recall bias. Most questionnaires were completed by the child's mother, however, and it is unlikely that a mother would not remember the breastfeeding history of her child. Even if errors occurred in the recall or reporting of breastfeeding duration, misclassification is unlikely to differ across exposure categories.

Although we adjusted for a variety of potential confounding factors, it is possible that unmeasured confounders, such as environmental factors and preterm birth, might have influenced the observed associations.

We confirmed an inverse association between breastfeeding duration regardless of exclusivity and asthma, but not wheeze; however, no evident relationships were observed between exclusive breastfeeding duration and asthma or wheeze. These data suggest that longer breastfeeding duration regardless of exclusivity is likely to be important in asthma prevention among children, especially those with parental allergic history. We acknowledge the need to verify our results by means of additional prospective studies in Asian countries.

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## Declaration of interest

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