

Effect of prolonged breast-feeding on risk of atopic dermatitis in early childhood

Soyoung Hong, M.P.H.,¹ Won-Jun Choi, M.D., M.P.H.,² Ho-Jang Kwon, M.D., Ph.D.,³ Yoon Hee Cho, M.P.H., Ph.D.,⁴ Hye Yung Yum, M.D., Ph.D.,⁵ and Dong Koog Son, Ph.D.⁶

ABSTRACT

The effect of breast-feeding on the risk of developing atopic disease remains controversial. This study is an investigation of the effect of breast-feeding on current atopic dermatitis (AD) among Korean children. This cross-sectional study of children's histories of current AD and environmental factors was completed by the subjects' parents. The subjects included 10,383 children aged 0–13 years in Seoul, Korea, in 2008. The diagnostic criteria of the International Study of Asthma and Allergies in Childhood were applied in this study. Adjustments were performed for age, gender, maternal education, smoking in the household, relocation to a new house within 1 year of birth, and parental history of atopic disease. After adjustment for confounders, age and duration of maternal education were found to be inversely associated with the prevalence of AD. Among subjects aged ≤ 5 years, the prevalence of AD was positively associated with the duration of breast-feeding ($p < 0.001$). However, there was no significant association between AD and breast-feeding among children > 5 years of age. Regardless of parental history of atopic diseases, breast-feeding > 12 months was a significant risk factor for AD. The effect of breast-feeding differed by age group. Prolonged breast-feeding increased the risk of AD in children < 5 years of age, regardless of parental history of atopic diseases.

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Atopic dermatitis (AD) is a common allergic skin disorder that is genetically transmitted, causes chronic inflammation, and affects up to 20% of children worldwide.¹ AD is often the initial manifestation of atopy within an allergic reaction and also is a sign for an accompanying disease such as allergic rhinitis, asthma, or food allergy, which has been associated in almost one-third of cases in children.² Genetic and environmental factors are well known to regulate AD, but causes and/or mechanism of the development of AD are still unclear.

Breast-feeding is the preferred method of providing nutrition for infants in most cases because breast milk is thought to be superior to cow's milk in nutritional, immunologic, and psychological aspects.^{3–5} However, breast-feeding is one of the most highly controversial factors with respect to its effects on allergic diseases.

Although several studies reported that breast-feeding is protective against atopic diseases,^{6–8} the argument has been made that breast-feeding is a risk factor for allergic diseases.^{9,10} There are also studies showing no significant relationship between breast-feeding and atopic disorders.^{11,12}

These conflicting conclusions could exist because of the selection, or lack thereof, of different confounding factors, such as the subjects' age during the outcomes addressed and family histories of atopic disorders.^{13–16} The effect of breast-feeding on AD also appears to differ by age group. The studies with younger children usually showed protective effects of breast-feeding on atopic diseases, whereas increased risk tended to be reported from studies in which subjects were in late childhood or early adulthood.^{13,17} In most of the previous studies, however, the subjects' age ranges were limited. There have been insufficient studies that covered a wide range of age groups simultaneously. Moreover, familial history of allergic diseases is one of the most important risk factors for the development of atopic disorders in children, and adjustment for parental history was only performed in some of the previous studies.¹⁷

In particular, there is insufficient epidemiological data about the relationship between breast-feeding and AD in Korean populations. A cross-sectional study with a large number of children of varying age was performed to determine the association between breast-feeding and the prevalence of AD symptoms during the past 12 months for children in Seoul, Korea.

From the ¹Department of Environmental Health Research, Seoul Medical Center, Seoul, Republic of Korea, ²Department of Occupational and Environmental Medicine, Gachon University Gil, Medical Center, Incheon, Republic of Korea, ³Department of Preventive Medicine, College of Medicine, Dankook University, Cheonan, Republic of Korea, ⁴Center for Environmental Health Sciences, Department of Biomedical and Pharmaceutical Sciences, University of Montana, Missoula, Montana, ⁵Atopy Asthma Center, Seoul Medical Center, Seoul, Republic of Korea, and ⁶Health Insurance Policy Research Institute, National Health Insurance Service, Seoul, Republic of Korea. Funded by grants from the Seoul Medical Center, Research Institute. The authors have no conflicts of interest to declare pertaining to this article. Address correspondence to Ho-Jang Kwon, M.D., Ph.D., College of Medicine, Dankook University 330–714, Anseo-dong, Dongnam-gu, Cheonan, Chungcheongnam-do, Korea.

E-mail address: hojang@dankook.ac.kr

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METHODS

Study Design and Subjects

Subjects were recruited from 5 elementary schools and 73 preschools selected from 5 areas of Seoul, Korea (*i.e.*, central, northeast, northwest, southwest, and southeast). In total, 15,515 children responded to a questionnaire (response rate, 96.4%). After the exclusion of subjects with missing data, 10,383 (4834 boys [46.6%] and 5549 girls [53.4%]) children were ultimately included in the study. There were 1389 children from the central area, 2284 from the northeastern area, 2320 from the northwestern area, 2025 from the southwestern area, and 2365 from the southeastern area. Informed consent was given by the participants' parents, and the study protocol was approved by the institutional review boards of the Asan Medical Center and Hanyang University, Seoul, Korea.

Questionnaire Survey

We developed a structured questionnaire comprising gender, age, maternal school education (<13, 13–16, or >16 years), smoking in the household (yes/no), moving to a newly built house within 1 year after birth (yes/no), and parental history of atopic diseases (any of AD, asthma, and allergic rhinitis). Questionnaires included breast-feeding history and duration (none, <6 months, 6–12 months, or >12 months). After the content of the questionnaire was explained to the parents or guardians of the children, written consent was obtained. All of the questionnaires were also completed by parents or guardians and collected.

Outcomes

"Current AD" was the primary outcome in this analysis. Question items were derived from the International Study of Asthma and Allergies in Childhood core questionnaires.¹⁸ Current AD was defined as "yes" when all of following three questions were positively marked: (1) Has your child ever had an itchy rash that was coming and going for at least 6 months? (2) Has your child had this itchy rash at any time in the last 12 months? (3) Has this itchy rash at any time affected any of the following places: the folds of the elbows, behind the knees, in front of the ankles, under the buttocks, or around the neck, ears, or eyes?

Statistical Analysis

Cross-analysis of the subjects was performed and Pearson χ^2 -tests were conducted to compare proportions. Binary logistic regression was used to test the associations between the duration of breast-feeding and AD while controlling for risk factors. The associations between AD and risk factors are expressed as odds ratios (ORs) with 95% confidence intervals (CIs). To calculate a trend in the prevalence of AD

Table 1 General characteristics of the subjects (*n* = 10,383)

Characteristics	<i>n</i> (%)
Gender	
Boys	4834 (46.6)
Girls	5549 (53.4)
Age (yr)	
0–5	6373 (61.4)
6–13	4010 (38.6)
Maternal education	
<13 (high school)	2803 (27.0)
13–16 (university)	6565 (63.2)
>16 (graduate school)	1015 (9.8)
Smoking in the household	
Yes	4237 (40.8)
No	6146 (59.2)
Duration of breast-feeding (mo)	
None	2479 (23.9)
<6	4388 (42.3)
6–12	1577 (15.0)
>12	1959 (18.9)
Relocation to a new house within a year of birth	
Yes	1624 (15.7)
No	8759 (84.3)
Parental history of atopic disease	
Yes	4012 (38.6)
No	6371 (61.4)
Symptom prevalence of AD (last 12 mo)	1708 (16.4)

AD = atopic dermatitis.

according to age, maternal school education, and duration of breast-feeding, a general linear model was constructed. In all of the analyses, a value of $p < 0.05$ was regarded as statistically significant. Data analysis was conducted using STATA Version 10.0 (StataCorp, College Station, TX).

RESULTS

The distributions of the selected factors in 10,383 children are summarized in Table 1. There were 4834 (46.6%) male and 5549 (53.4%) female subjects. Subjects were 61.4% aged ≤ 5 and 38.6% 6- to 13-year olds. The most common duration of maternal education was 13–16 years (university level, 63.2%). Exposure to passive smoking in the household occurred in 4237 cases (40.8%). There were 2479 (23.9%) subjects who had never been fed breast milk, 4388 (42.3%) who were breast-fed for <6 months, 1577 (15.0%) for 6–12 months, and 1959 (18.9%) who were breast-fed >12 months. Moving to a newly built house within the 1st year after birth occurred in 1624 cases (15.7%). A family history of AD was observed in 38.6%. In this study, the prevalence of AD in the last 12 months was 16.4%.

Table 2 Unadjusted and adjusted ORs with 95% CIs for risk factors for AD

	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Gender		
Boys	1.00	1.00
Girls	1.06 (0.95–1.18)	1.07 (0.97–1.19)
Age (yr)		
0–5	1.00	1.00
6–13	0.61 (0.54–0.68)	0.64 (0.56–0.72)
Maternal school education (yr)		
<13	1.00	1.00
13–16	1.11 (0.98–1.25)	0.94 (0.83–1.07)
>16	1.01 (0.83–1.23)	0.80 (0.65–0.98)
<i>p</i> value for trend	0.44	0.04
Smoking in the household		
No	1.00	1.00
Yes	1.02 (0.91–1.13)	1.07 (0.97–1.20)
Duration of breast-feeding (mo)		
None	1.00	1.00
<6	1.16 (1.01–1.34)	1.00 (0.86–1.16)
6–12	1.35 (1.13–1.60)	1.21 (1.01–1.44)
>12	1.75 (1.49–2.04)	1.44 (1.22–1.70)
<i>p</i> Value for trend	<0.001	<0.001
Relocation to a new house within 1 yr of birth		
No	1.00	1.00
Yes	1.46 (1.28–1.67)	1.40 (1.23–1.60)
Parental history of atopic diseases		
No	1.00	1.00
Yes	1.54 (1.39–1.71)	1.48 (1.33–1.65)

AD = atopic dermatitis; CI = confidence interval; OR = odds ratio.

The ORs and 95% CIs for the risk factors are presented in Table 2. Both unadjusted and adjusted ORs were calculated. There was little difference in the results after adjustment. In the adjusted model, gender was not a significant variable. The prevalence of AD was inversely associated with age (OR = 0.64; 95% CI, 0.56–0.72). Compared with the non-breast-fed group, the prevalence of AD was 1.21-fold increased with breast-feeding of 6–12 months and 1.44-fold increased with breast-feeding of >12 months (95% CI, 1.01–1.44 and 1.22–1.70, respectively). The prevalence of AD was positively associated with the duration of breast-feeding ($p < 0.001$). Moving to a newly built house within 1 year after birth was a significant risk factor (OR = 1.40;

95% CI, 1.23–1.60). Parental history of AD was also significant (OR = 1.48; 95% CI, 1.33–1.65).

Table 3 shows that the effect of breast-feeding differed by age but not by parental history of atopic diseases. Among subjects aged ≤ 5 years, the prevalence of AD was increased 1.56-fold in subjects with prolonged breast-feeding (*i.e.*, >12 months) when compared with those who never breast-fed (95% CI, 1.26–1.94). The prevalence of AD was positively associated with the duration of breast-feeding ($p < 0.001$). However, among subjects >5 years of age, no significant association between AD and the duration of breast-feeding was observed ($p = 0.07$). The effect of breast-feeding on AD was not modified by parental history of atopic diseases.

DISCUSSION

In this study, the duration of breast-feeding was positively associated with an increased risk of AD in children aged ≤ 5 years. There was a clear dose-response relationship even after adjustment for other risk factors. The results of the present study were consistent with other previous studies that concluded that an increased risk for AD with increased duration of breast-feeding was observed.^{19,20} An increased risk of atopic diseases associated with breast-feeding was also consistently established.^{13,21–23}

There are some plausible explanations regarding the mechanism underlying these results: the transmission of risk factors through breast-feeding^{22,24–26} and genetic predisposition of individuals.^{27,28} Breast milk is known to contain various endocrine-disrupting chemicals²² and immunologically active substances such as allergens.²⁴ Polychlorinated dibenzo-*p*-dioxins and polychlorinated dibenzo-furans transmitted through breast-feeding may also induce allergic reactions.²² Certain cytokines such as IL-4, IL-8, RANTES, IgE, transforming growth factor β , and soluble CD-14 or polyunsaturated fatty acids have been suggested as inducers of the allergic reactions to develop allergic disorders in the infant recipient.^{25,26} Some studies reported that genetic factors such as fatty acid desaturases genes could modulate the development of allergic diseases.^{27,28} It is unclear how these complex mechanisms influence the development of atopic diseases, but genetic factors or gene-environmental interactions may play an important role and demand further research. Meanwhile, the variation between countries in breast milk's contamination with environmental toxins with possible immunomodulatory effects may suggest that studies should not be generalized to countries with different rates of breast-feeding and environmental factors.²⁹

In this study, the risk factors for AD differed between the two age groups. Breast-feeding was only a risk factor among the children who were ≤ 5 years of age. Previous studies revealed that there was no significant association between eczema or atopic diseases and

Table 3 Stratified multiple logistic regression analysis for associations between AD and risk factors

	Age ≤5 yr aOR ^a (95% CI)	Age >5 yr aOR ^a (95% CI)	Parental History (–) aOR ^b (95% CI)	Parental History (+) aOR ^b (95% CI)
Duration of breast-feeding (mo)				
None	1.00	1.00	1.00	1.00
<6	1.03 (0.85–1.26)	1.01 (0.80–1.26)	0.98 (0.81–1.18)	1.00 (0.80–1.26)
6–12	1.22 (0.96–1.55)	1.28 (0.97–1.68)	1.14 (0.90–1.44)	1.26 (0.96–1.65)
>12	1.56 (1.26–1.94)	1.25 (0.91–1.70)	1.45 (1.16–1.80)	1.38 (1.07–1.77)
<i>p</i> Value for trend	<0.001	0.07	<0.001	0.001

^aAdjusted for gender, maternal school education, smoking in the household, relocation to a new house within 1 year of birth, and parental history of atopic diseases.

^bAdjusted for gender, age, maternal school education, smoking in the household, and relocation to a new house within 1 year of birth.

AD = atopic dermatitis; CI = confidence interval; aOR = adjusted odds ratio.

breast-feeding in late childhood and early adulthood.^{30–32} It seems that the effect of breast-feeding on AD depends on age, but the reason for this relationship is unclear. One possible explanation is that the influence of improved immunity during development supersedes environmental factors in late childhood. In this study, environmental factors such as smoking in the household or relocation to a new house within the 1st year of birth increased the prevalence of AD among those aged ≤5 years but not >5 years old (data not shown). On the other hand, age was inversely associated with AD only among subjects >5 years of age. These results suggest that the influence of environmental factors including breast-feeding is greater in early childhood than in late childhood. Longitudinal prospective follow-up studies from infants to young adults are necessary to confirm this point of view.

Our results revealed that parental history of AD did not modify the effect of breast-feeding on AD. Parental history of atopic diseases is known as one of the most important confounders affecting both AD of children and breast-feeding itself.²¹ Sabin *et al.* discussed breast-feeding for at least 4 months as a reducing factor in infancies who are high risk for AD.³³ A review performed by Gdalevich *et al.* also showed that breast-feeding in the first 3 months after birth significantly reduce AD in patients with a positive family history.³⁴ However, Dattner stated that the effect of breast-feeding during the first 4 months of life for reducing AD is questionable, especially in cases when the mother herself is allergic.³⁵ Furthermore, he suggested an allergen-avoidance diet such as probiotic and essential fatty acid supplementation may reduce the chance of maternal dietary allergens provoking infant AD. Another recent study also supported that probiotic supplementation plays a role in preventing AD development and reducing its severity.³⁶ In addition, the rate of breast-feeding was associated with parental history of AD,³⁷

and the duration of breast-feeding would be longer if parents who had atopic diseases believed that breast-feeding could reduce or prevent atopic disease in their children.^{38,39} If so, children who were at high risk of atopic disease received prolonged breast-feeding and, thus, a so-called reverse causation would arise. However, the distribution of duration of breast-feeding was very similar within the two groups separated by family history of atopic diseases (data not shown). Therefore, reverse causation would be less likely in this study.

The limitation of cross-sectional nature of this study and dependence on parent report for children's allergic symptoms rather than pediatric physicians limited this study to reliably showed a temporal relationship between AD and breast-feeding. The subjects studied in the present study might not represent the children and adolescents in Seoul, because of convenience sampling. Recall bias may have arisen because some the questions were about events that happened several years earlier. In addition, we did not classify whether breast-feeding was exclusive or partial. However, regardless of the type of breast-feeding (exclusive or partial), prolonged breast-feeding was also associated with an increased prevalence of AD in a Japanese study.³⁹

Despite several limitations, to our best knowledge, this is the first study of the association between breast-feeding and AD in Korean children. A large number of subjects of a wide age range were also enrolled and recruited from a relatively homogenous residential background (*i.e.*, the largest city in Korea) in this study. Several important confounding factors that could affect the relationship between breast-feeding and AD were also considered. The questionnaire used in this study was based on the International Study of Asthma and Allergies in Childhood written questionnaire, which is a standardized tool used worldwide.

In conclusion, breast-feeding increases the risk of AD, particularly among children aged ≤5 years, regardless of

parental history of atopic diseases. Long-term follow-up studies should be emphasized to determine the temporal relationship between breast-feeding and atopic diseases.

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