Breast-feeding does not protect against allergic sensitization in early childhood and allergy-associated disease at age 7 years

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Background: Extended breast-feeding is recommended for newborn children at risk of allergy-associated diseases, but the evidence of a protective effect on sensitization and these diseases remains elusive.

Objective: The aim of this study was to investigate the effects of the duration of exclusive breast-feeding on the development of sensitization in preschool children.

Methods: Information on breast-feeding was gathered by interviews involving 335 children aged 1, 6, and 12 months from the Copenhagen Prospective Study on Asthma in Childhood$_{2000}$ birth cohort born to mothers with a history of asthma. Skin prick test responses and specific IgE levels against 12 common inhalant and 10 food allergens were assessed longitudinally at ages ½ year, 1½ years, 4 years, and 6 years. Eczema, wheeze/asthma, and allergic rhinitis were diagnosed at the Copenhagen Prospective Studies on Asthma in Childhood clinic at 7 years of age, strictly adhering to predefined algorithms. Associations between duration of exclusive breast-feeding and outcomes were analyzed by logistic regression.

Results: We found no significant association between duration of exclusive breast-feeding and development of sensitization in the first 6 years of life (odds ratio [OR]: ½ year, 1.10 [95% CI, 0.90-1.36]; 1½ years, 1.15 [95% CI, 0.97-1.36]; 4 years, 1.08 [95% CI, 0.93-1.25]; and 6 years, 0.96 [95% CI, 0.84-1.10]) or with current eczema, wheeze/asthma, and allergic rhinitis at age 7 years (OR, 1.07 [95% CI, 0.92-1.24]; OR, 0.97 [95% CI, 0.82-1.14]; and OR, 1.02 [95% CI, 0.84-1.23], respectively). Adjusting for reverse causation by excluding children with eczema, wheeze, or a positive skin prick test response before ending exclusive breast-feeding did not alter the results.

Conclusion: Exclusive breast-feeding does not affect sensitization in early childhood or associated diseases at 7 years of age in at-risk children. (J Allergy Clin Immunol 2015;■■■:■■■-■■■.)

Key words: *Breast-feeding, sensitization, asthma, eczema, skin prick test, specific IgE, children*

The beneficial effects of breast-feeding on allergy-associated diseases have been debated since an American study of 20,061 children from 1936[1] reported a protective effect of breast-feeding on the development of eczema. In particular, it is recommended that high-risk children should be offered a prolonged duration of exclusive breast-feeding or hydrolyzed substitution.[2-4]

It appears intuitively sensible to avoid allergens in early life to avoid sensitization, allergy, and maybe even allergy-related disorders. However, the evidence on such associations has been conflicting, with some reporting a protective effect on the development of allergy-associated diseases,[5-7] others reporting no effect,[8,9] and some even reporting an increase in risk.[10-13]

Reverse causation might explain the conflicting results. This can lead to misinterpretation of the results, showing an increased risk of allergy-associated diseases with prolonged breast-feeding, when in fact it is the development of allergy-associated disease that leads mothers to extend breast-feeding.[14] We have previously reported that exclusive breast-feeding reduced the risk of wheezy disorders, but, surprisingly, increased the risk of eczema at the age of 2 years.[10]

This study aimed to analyze the effect of duration of breast-feeding on the development of sensitization during the first 6 years of life. In addition, we investigated the long-term effect of breast-feeding on eczema, wheeze/asthma, and allergic rhinitis at 7 years of age in the longitudinal high-risk birth cohort Copenhagen Prospective Studies on Asthma in Childhood$_{2000}$ (COPSAC$_{2000}$).

METHODS

Design

The COPSAC$_{2000}$ birth cohort is a single-center prospective clinical birth cohort study of 411 children born between August 1998 and December 2001 to mothers with a history of asthma. The children were enrolled at 1 month of age and closely monitored by scheduled 6-month visits at the clinical research unit until the age of 7 years. At each visit, the children were followed with comprehensive clinical investigations according to standard operating procedures, and clinical outcomes were diagnosed and monitored by the COPSAC physicians. The families also used the clinical research unit instead of the family practitioner for diagnosis and treatment of any acute episodes of lung, skin, or allergy-related symptoms. The recruitment and baseline characteristics of the participants have been described in detail.[15-17]

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The Copenhagen Prospective Studies on Asthma in Childhood (COPSAC) is funded by private and public research funds, all of which are listed at www.copsac.com. The Lundbeck Foundation (R16-A1694); the Ministry of Health (grant no. 903516); the Danish Council for Strategic Research (grant no. 0603-00280B); the Danish Council for Independent Research (grant no. 10-082884; 271-08-0815); and the Capital Region Research Foundation have provided core support for COPSAC. Thermo Fisher Scientific Inc sponsored the IgE analyses. No pharmaceutical company was involved in the study. The funding agencies did not have any role in design and conduct of the study; collection, management, and interpretation of the data; or preparation, review, or approval of the manuscript.

Disclosure of potential conflict of interest: H. Bisgaard has received research support from the Lundbeck Foundation, the Danish Ministry of Health, and the Danish Strategic Research Foundation. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication September 25, 2014; revised February 14, 2015; accepted for publication February 22, 2015.

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0091-6749/$36.00

http://dx.doi.org/10.1016/j.jaci.2015.02.023

Abbreviations used
COPSAC: Copenhagen Prospective Studies on Asthma in Childhood
IHRP: In-house reference preparation
OR: Odds ratio
sIgE: Specific IgE
SPT: Skin prick test

The Copenhagen Ethics Committee (KF 01-289/96) and the Danish Data Protection Agency (2008-41-2434) approved the study, and informed consent was obtained from both parents at enrollment.

Breast-feeding

Information on breast-feeding was collected prospectively by experienced research personnel who interviewed the mothers at the 1-, 6-, and 12-month clinical visits about the duration of exclusive and total breast-feeding and the use of infant formula. As soon as the child's diet was supplemented by even short periods of supplementation with formula, we considered exclusive breast-feeding to be terminated. It was standard procedure in the maternity ward to supply a hypoallergenic milk supplement until breast-feeding was established. Children receiving hypoallergenic formula for more than 7 days before establishing breast-feeding were excluded from this study because they were registered as never having been fully breast-fed.

Allergic sensitization

Skin prick tests (SPTs) and specific IgE (sIgE) measurements were performed at ½, 1½, 4, and 6 years of age against 10 food and 12 inhalant allergens (see Table E1 in this article's Online Repository at www.jacionline.org).

Serum sIgE levels were determined by using a screening method (ImmunoCAP Phadiatop Infant and ImmunoCAP Phadiatop; Thermo Fisher Scientific, Waltham, Mass),[18] followed by analyses of sIgE levels against single allergens. sIgE values of 0.35 kU_A/L or greater were considered indicative of sensitization.[17]

SPTs were performed on the children's volar forearm with standard allergen extracts (Soluprick SQ; ALK, Hørsholm, Denmark) and ALK lancets. ALK standardizes every lot of allergen extract by using an in-house reference preparation (IHRP). This IHRP is thoroughly characterized, including tests on patients, and each new batch is compared with the IHRP by using appropriate laboratory tests. These include tests for complexity, major allergen content, and IgE-binding capacity. All SPTs were done by the same experienced research personnel. The positive control was read after 10 minutes, and the negative control and reactions to allergen extracts were read after 15 minutes. The average of 2 perpendicular wheal diameters was noted, and a test result was defined as positive with a wheal size at least 2 mm greater than that elicited by the negative control at ages ½ and 1½ years and at least 3 mm greater than that elicited by the negative control at age 4 and 6 years.

Children did not use antihistamines within 72 hours of testing (a positive control was used as screening for use of antihistamines with longer half-life), mild steroid creams (group 1-2) on the arms 24 hours before testing or stronger steroid creams (group 3-4) 14 days before testing.

We defined allergic sensitization as a positive SPT response, a positive sIgE level, or both.

Asthma and recurrent wheeze

The diagnosis of asthma by age 7 years was based on 4 mandatory criteria. The first was a history of recurrent wheeze, as defined by our strict algorithms. Daily symptoms were recorded from birth by parents and discussed with the accompanying parent by the COPSAC physicians at planned and acute visits. A wheezy episode was defined from the diary card as 3 consecutive days of troublesome lung symptoms that seriously hampered the well-being of the child, including cough, wheeze, or breathlessness, which was thoroughly explained to the parents at the regular clinic visits, as well as described in written material. Recurrent wheeze was defined as 5 wheezy episodes within 6 months, daily symptoms for 4 successive weeks, or acute severe asthma symptoms resulting in hospitalization or the need for systemic corticosteroid treatment.[16,17]

The second criterion was the presence of symptoms judged by the COPSAC physicians to be typical of asthma (eg, exercise-induced symptoms, prolonged nocturnal cough, recurrent cough outside common cold, and symptoms causing wakening at night).

The third criterion was need for intermittent rescue use of inhaled β_2-agonists.

The fourth and final criterion was response to a 3-month program of daily inhaled corticosteroids and relapse after treatment's end.

Allergic rhinitis

The diagnosis of allergic rhinitis in the seventh year of life was based on 2 criteria. The first was a history of symptoms based on parental interviews. Symptoms were defined as significant problems with sneezing or blocked or runny nose in the past 12 months in periods outside the common cold or flu. The second criterion was sensitization to allergens associated with relevant symptoms on exposure.[19] Symptoms without association to documented sensitization were diagnosed as nonallergic rhinitis.

Eczema

Eczema was diagnosed according to the Hanifin and Rajka criteria,[20] which are based on the presence of 3 of 4 major criteria and at least 3 of 23 minor signs. The major criteria are (1) pruritus, (2) typical morphologic features and distribution, (3) chronic dermatitis, and (4) atopic history. The diagnosis was made by the physicians at the clinical research unit. Of the minor signs in the criteria, the following 6 were excluded: sensitization verified by SPT responses or sIgE levels, keratoconus and anterior subcapsular cataracts (because they required identification by an ophthalmologist), delayed blanch (because it required an injection of methacholine), and impaired cell-mediated immunity.

Eczema was assessed longitudinally from birth to age 7 years, defining both age of debut and end.[21]

Statistical methods

Dropout analyses were performed by using the χ^2, Student *t*, and Wilcoxon rank sum tests. Associations between duration of exclusive breast-feeding and sensitization, eczema, wheeze/asthma, and allergic rhinitis were analyzed by logistic regression. For power analyses, see the Methods section in this article's Online Repository at www.jacionline.org.

Exclusive breast-feeding was classified as months of breast-feeding and investigated as a continuous trait, and each health outcome was dichotomized as yes or no. Sensitization was investigated at ages ½, 1½, 4, and 6 years.

Eczema, wheeze/asthma, and allergic rhinitis were investigated at age 7 years. Data on recurrent wheeze and asthma were combined and analyzed as one outcome.

Children with incomplete data (missing values on either health outcome or breast-feeding) and those who were never exclusively breast-fed (n = 22) were excluded from the analyses.

The results are presented as odds ratios (ORs) and 95% CIs by each additional month of exclusive breast-feeding. All corresponding *P* values were estimated by using Wald tests.

The robustness of the results was evaluated by redoing the analyses with breast-feeding as a categorical variable, dichotomizing duration of breast-feeding into categories of more or less than 4 months, and more or less than 6 months.

Subgroup analyses were done by evaluating the effect of breast-feeding in children with a double disposition to allergy-associated diseases, by only analyzing children with both parents with allergy-associated disease. Analyses were additionally done including only children born to mothers with positive sIgE levels.