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**Effect of prolonged and exclusive breast feeding on risk of allergy and asthma: cluster randomised trial**

Michael S Kramer, Lidia Matush, Irina Vanilovich, Robert Platt, Natalia Bogdanovich, Zinaida Sevkovskaya, Irina Dzikovich, Gyorgy Shishko, Bruce Mazer

**ABSTRACT**

Objective To assess whether exclusive and prolonged breast feeding reduces the risk of childhood asthma and allergy by age 6.5 years.

Design Cluster randomised trial.

Setting 31 Belarusian maternity hospitals and their affiliated polyclinics.

Participants A total of 17 046 mother-infant pairs were enrolled, of whom 13 889 (81.5%) were followed up at age 6.5 years.

Intervention Breastfeeding promotion intervention modelled on the WHO/UNICEF baby friendly hospital initiative.

Main outcome measures International study of asthma and allergies in childhood (ISAAC) questionnaire and skin prick tests of five inhalant antigens.

Results The experimental intervention led to a large increase in exclusive breast feeding at 3 months (44.3% v 6.4%; P<0.001) and a significantly higher prevalence of any breast feeding at all ages up to and including 12 months. The experimental group had no reduction in risks of allergic symptoms and diagnoses or positive skin prick tests. In fact, after exclusion of six sites (three experimental and three control) with suspiciously high rates of positive skin prick tests, risks were significantly increased in the experimental group for four of the five antigens.

Conclusions These results do not support a protective effect of prolonged and exclusive breast feeding on asthma or allergy.

**EDITORIAL by Gahagan**

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Functional physiotherapy exercise soon after discharge results in short term benefit after elective primary knee arthroplasty. No benefit was seen at one year.
healthy mothers and infants to breast feeding versus formula feeding is infeasible and unethical, randomising them to an intervention that promotes breast feeding is both feasible and ethical. We developed a strategy to promote exclusivity and duration of breast feeding for the promotion of breastfeeding intervention trial (PROBIT), a cluster randomised trial in the Republic of Belarus. We describe the methods and results of measures of allergic symptoms and diagnoses and skin prick tests after 6.5 years of follow-up among Belarusian children enrolled in PROBIT.

**METHODS**

The units (clusters) of randomisation were maternity hospitals and one affiliated polyclinic for each hospital. The experimental intervention was based on the baby friendly hospital initiative, developed by the World Health Organization (WHO) and the United Nations Children’s Fund (UNICEF) to promote and support breast feeding. The control maternity hospitals and polyclinics continued the practices in effect at the time of randomisation. The trial results are based on a total of 17 046 healthy breastfed infants from 31 maternity hospitals/polyclinics.

The two randomised groups were similar in baseline sociodemographic and clinical variables. The experimental intervention led to a substantial difference in the duration of any breast feeding that was maintained throughout the first year of follow-up: 72.7% versus 60.0% were still breast feeding at 3 months, 49.8% versus 36.1% at 6 months, 36.1% versus 24.4% at 9 months, and 19.7% versus 11.4% at 12 months in the experimental and control groups. The prevalence of exclusive breast feeding was sevenfold higher in the experimental group at 3 months (43.3% v 6.4%; P<0.001), although low in both groups at 6 months (7.9% v 0.6%; P=0.01).

Paediatricians in the polyclinics did follow-up interviews and examinations at age 6.5 years from December 2002 to April 2005. Allergy symptoms and diagnoses were ascertained with the international study of asthma and allergy in childhood (ISAAC) questionnaire. Paediatricians did skin prick tests to five antigens: house dust mite, cat, birch pollen, mixed northern grasses, and Alternaria. Because of a paper that was published on bmj.com on 11 September 2007. Cite this version as: BMJ 2007;335:815-8

**RESULTS**

A total of 13 889 children were seen in follow-up for PROBIT II, representing 81.5% of the 17 046 originally randomised. Follow-up rates were similar in the experimental (80.2%) and control (82.9%) polyclinics but varied considerably by polyclinic. The mean age at follow-up was 6.6 (SD 0.3) years. The children followed up in the experimental and control groups were similar in baseline characteristics.

The audit results showed high k coefficient values for wheezing and hay fever symptoms and moderate values for reported diagnosis of asthma or symptoms and diagnosis of atopic eczema. Concordance was high for the skin prick test results, but only 54 (28%) of the 190 audited children agreed to the repeat skin tests. Table 1 shows the trial results for the ISAAC questionnaire. The results showed a low degree of clustering. Most of the symptoms and diagnoses were slightly more prevalent in the experimental group than in the control group, but the cluster adjusted odds ratios in the experimental versus control groups were close to unity for all of the symptoms and diagnoses.

Table 2 shows the skin prick test results. Of the 13 889 PROBIT children seen at follow-up, 11 772 (85%) agreed to the skin prick tests, of whom 11 146 (95%) had valid results. Positive skin test results were slightly but consistently more frequent in the experimental group for all five test antigens, although none of the differences was statistically significant.

Skin prick test results were extremely variable and highly clustered among the 31 polyclinics. Six of the polyclinics (three experimental and three control) had positivity rates of ≥10% to each of the five test antigens, considerably higher than those at the 25 other polyclinics.

We did a sensitivity analysis (n=9006) after excluding the six polyclinic sites with high rates of positive skin prick test results (table 3). Intraclinic clustering of skin prick test results was reduced substantially. The proportions of positive test results were considerably lower in both the experimental and control groups, yet the differences between the two groups increased, with significantly elevated odds ratios in the 2-3 range for all but one antigen (mixed northern grasses).

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**Table 1** ISAAC results. Values are numbers (percentages) positive unless stated otherwise

<table>
<thead>
<tr>
<th>Question</th>
<th>Experimental group (n=7101)</th>
<th>Control group (n=6763)</th>
<th>ICC</th>
<th>Cluster adjusted odds ratio* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ever had wheezing</td>
<td>778 (11.0)</td>
<td>651 (9.6)</td>
<td>0.03</td>
<td>1.1 (0.6 to 1.8)</td>
</tr>
<tr>
<td>Wheezing in past 12 months</td>
<td>238 (3.4)</td>
<td>188 (2.8)</td>
<td>0.01</td>
<td>1.0 (0.7 to 1.6)</td>
</tr>
<tr>
<td>Ever had asthma</td>
<td>97 (1.4)</td>
<td>68 (1.0)</td>
<td>0.00</td>
<td>1.2 (0.7 to 1.9)</td>
</tr>
<tr>
<td>Ever had hay fever symptoms</td>
<td>384 (5.4)</td>
<td>257 (3.8)</td>
<td>0.02</td>
<td>1.1 (0.6 to 1.9)</td>
</tr>
<tr>
<td>Hay fever symptoms in past 12 months</td>
<td>262 (3.7)</td>
<td>192 (2.8)</td>
<td>0.01</td>
<td>1.0 (0.6 to 1.8)</td>
</tr>
<tr>
<td>Recurrent itchy rash</td>
<td>350 (4.9)</td>
<td>241 (3.6)</td>
<td>0.02</td>
<td>1.3 (0.7 to 2.2)</td>
</tr>
<tr>
<td>Ever had eczema</td>
<td>69 (1.0)</td>
<td>72 (1.1)</td>
<td>0.00</td>
<td>1.0 (0.5 to 1.8)</td>
</tr>
</tbody>
</table>

ICC=intraclass correlation coefficient. *For experimental group versus control group.
Table 2 | Skin prick test results. Values are numbers (percentages) positive unless stated otherwise

<table>
<thead>
<tr>
<th>Antigen</th>
<th>Experimental group (n=5551)</th>
<th>Control group (n=5595)</th>
<th>ICC</th>
<th>Cluster adjusted odds ratio* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>House dust mite</td>
<td>805 (14.5)</td>
<td>603 (10.8)</td>
<td>0.14</td>
<td>1.1 (0.5 to 2.4)</td>
</tr>
<tr>
<td>Cat</td>
<td>648 (11.7)</td>
<td>491 (8.8)</td>
<td>0.20</td>
<td>1.2 (0.5 to 2.8)</td>
</tr>
<tr>
<td>Birch pollen</td>
<td>526 (9.5)</td>
<td>393 (7.0)</td>
<td>0.18</td>
<td>1.2 (0.5 to 2.9)</td>
</tr>
<tr>
<td>Mixed northern grasses</td>
<td>712 (12.8)</td>
<td>491 (8.8)</td>
<td>0.17</td>
<td>1.0 (0.5 to 2.3)</td>
</tr>
<tr>
<td>Alternaria</td>
<td>480 (8.6)</td>
<td>340 (6.1)</td>
<td>0.18</td>
<td>1.5 (0.5 to 4.4)</td>
</tr>
<tr>
<td>≥1 positive</td>
<td>1496 (27.0)</td>
<td>1013 (18.1)</td>
<td>0.19</td>
<td>1.2 (0.5 to 2.6)</td>
</tr>
</tbody>
</table>

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*For experimental group versus control group.

Statistical models with interaction terms showed no evidence of protective effects of the experimental intervention on allergic symptoms and diagnoses or skin prick tests in children with or without a positive family history of atopy. In observational analyses (that is, ignoring the randomised treatment allocation), we found borderline significant reductions in history of eczema both with more prolonged any breast feeding and with more prolonged exclusive breast feeding (P=0.08 for both associations, based on χ² tests for trend). We found highly significant increases in positive skin prick test results with exclusive breast feeding for 3 to <6 months and ≥6 months versus <3 months for house dust mite, cat, birch pollen, mixed northern grasses, and Alternaria (P<0.001 for all five antigens, based on χ² tests for trend).

DISCUSSION

The results from this large cluster randomised trial indicate that the experimental intervention to promote prolonged and exclusive breast feeding did not reduce the risk of asthma, hay fever, or eczema at age 6.5 years despite large increases in the duration and exclusivity of breast feeding; nor did the intervention succeed in reducing the prevalence of positive skin prick tests. We observed high inter-paediatrician variability in results of skin prick tests. After exclusion of six polyclinics with suspiciously high rates of positive skin prick test results, the relative odds of positive skin prick tests were twofold to threefold higher in the experimental group than in the control group.

These results conflict with some previous studies suggesting that prolonged and exclusive breast feeding reduces the risk of asthma, other allergic diseases, and positive atopy skin tests. On the other hand the evidence is far from uniform, and several recent studies have even found breast feeding to be associated with increased risks of these outcomes. Some investigators have found stronger protective effects of breast feeding in offspring with a positive family history of atopy, but we did not. The prevalences of all allergic symptoms and diagnoses were lower among PROBIT children than are customarily seen in Western industrialised countries but similar to those previously reported from Eastern Europe. Caution is therefore advised in extrapolating our results to settings where atopic diseases occur more frequently.

The absence of a protective effect against eczema also conflicts with our previous findings based on follow-up during infancy. The extremely low reported histories of eczema at 6.5 years (table 1), however, are likely to be gross underestimates. These histories may reflect the absence of an eczema “label” transmitted to the parents but almost certainly constitute a less objective result than that previously reported from PROBIT. The finding of exceedingly high rates of positive skin tests at six of the study sites, equally divided between experimental and control groups, is not easily explained. Something systematic clearly occurred at these sites, leading to our decision to eliminate them in the sensitivity analysis. These six study sites had no obvious links and were dispersed geographically. The six sites did not have higher prevalences of allergic symptoms than the 25 sites with much lower skin prick test positivity rates. Skin testing is influenced by the technique of the tester, but all testers were trained by the same investigator and received the same equipment.

Given that we found significantly increased risks of positive skin prick tests in the experimental group only after excluding the six suspect polyclinics, we cannot be confident that the experimental intervention actually caused the increased risks. We feel on safer ground in inferring no reduction in risk. Given these results based on a large randomised trial and the inconsistent benefits reported in previous studies, public health measures to increase the initiation, duration, and exclusivity of breast feeding seem unlikely to have a major impact on reducing the incidence of atopic diseases.

Table 3 | Results of sensitivity analysis for skin prick test results. Values are numbers (percentages) positive unless stated otherwise

<table>
<thead>
<tr>
<th>Antigen</th>
<th>Experimental group (n=4100)</th>
<th>Control group (n=4906)</th>
<th>ICC</th>
<th>Cluster adjusted odds ratio* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>House dust mite</td>
<td>504 (12.3)</td>
<td>299 (6.1)</td>
<td>0.04</td>
<td>2.0 (1.2 to 3.4)</td>
</tr>
<tr>
<td>Cat</td>
<td>347 (8.5)</td>
<td>182 (3.7)</td>
<td>0.05</td>
<td>2.1 (1.1 to 3.9)</td>
</tr>
<tr>
<td>Birch pollen</td>
<td>273 (6.7)</td>
<td>125 (2.5)</td>
<td>0.03</td>
<td>2.3 (1.3 to 4.1)</td>
</tr>
<tr>
<td>Mixed northern grasses</td>
<td>369 (9.0)</td>
<td>209 (4.3)</td>
<td>0.06</td>
<td>1.5 (0.8 to 2.8)</td>
</tr>
<tr>
<td>Alternaria</td>
<td>258 (6.3)</td>
<td>77 (1.6)</td>
<td>0.05</td>
<td>3.5 (1.6 to 7.7)</td>
</tr>
<tr>
<td>≥1 positive</td>
<td>929 (22.7)</td>
<td>579 (11.8)</td>
<td>0.07</td>
<td>2.0 (1.1 to 3.4)</td>
</tr>
</tbody>
</table>

ICC=intraclass correlation coefficient.
*For experimental group versus control group.
WHAT IS ALREADY KNOWN ON THIS TOPIC

Evidence is conflicting as to whether prolonged and exclusive breast feeding increases, decreases, or has no effect on the risks of asthma and allergy. All of the available evidence is based on observational studies.

WHAT THIS STUDY ADDS

Prolonged and exclusive breast feeding had no protective effect on allergic symptoms and diagnoses or on positive skin prick tests.

Competing interests: None declared.

Ethical approval: The research ethics board of the Montreal Children’s Hospital of the McGill University Health Centre approved this project (including the 6.5 year follow-up).

Provenance and peer review: Non-commissioned; externally peer reviewed.


Accepted: 27 July 2007

Clint’s favourite question

Clint is an interviewer for a study investigating the relation between poverty and blindness in the Philippines. His parents were keen film fans and named their son after their hero Clint Eastwood. During the fieldwork, Clint and his friend Erwin slept in a tent in the living room of the house they would ask. Clint mentioned that the interviewees were very serious about their poverty and quality of life. Each interview lasted about an hour and included a long list of questions about jokes about *Brokeback Mountain*. Clint’s task was to interview people visually impaired from cataract, and controls matched for age and sex, about their poverty and quality of life. Each interview lasted about an hour and included a long list of questions about food and other things that the household spent money on each month. People were also asked about their general wellbeing, how they spent their time, and how their vision affected their life.

I asked Clint about his least favourite part of the interview. Not surprisingly, he mentioned the expenditure data, as this section is long and tedious. And his favourite part? He quickly responded, “When I ask them how much they would be able to rent out their house for.” Almost all the study participants were very poor and lived in rural areas, often in shacks that they had built themselves.

We welcome articles up to 600 words on topics such as *A memorable patient, A paper that changed my practice, My most unfortunate mistake, or any other piece conveying instruction, pathos or humour. Please submit the article on http://submit.bmj.com*. Permission is needed from the patient or a relative if an identifiable patient is referred to. We also welcome contributions for “Endpieces,” consisting of quotations of up to 80 words (but most are considerably shorter) from any source, ancient or modern, which have appealed to the reader.

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