

WHAT IS ALREADY KNOWN ON THIS TOPIC

Osteoarthritis is the commonest cause of disability in older people, and total knee joint arthroplasty is a common orthopaedic procedure

Uncertainty exists regarding whether physiotherapy after discharge should be routinely provided to patients after elective primary knee arthroplasty for osteoarthritis

WHAT THIS STUDY ADDS

Functional physiotherapy exercise soon after discharge results in short term benefit after elective primary knee arthroplasty

No benefit was seen at one year

discharge. In the short term physiotherapy exercise interventions with exercises based on functional activities may be more effective after total knee arthroplasty than traditional exercise programmes.

We thank Robert Bourne, David Beverland, P Codine, Helen Frost, Patricia Humphreys, John Kramer, and Brian Mockford for providing additional data for the review. Mike Clarke and students on the "Systematic Reviews" Module, May 2005, University of Oxford Department for Continuing Education, commented on the design of the review during its planning.

Contributors: See bmj.com.

Funding: CJML is funded by a nursing and allied health professional researcher development award from the Department of Health and NHS research and development. CMS is funded by a primary care career scientist award from the Department of Health and NHS research and development.

Competing interests: None declared.

Ethical approval: Oxford local research ethics committee (AQREC No A03.018).

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

- 1 National Audit Office. *Hip replacements: an update*. London: Stationery Office, 2003 (HC 956).
- 2 Noble PC, Gordon MJ, Weiss JM, Reddix RN, Conditt MA, Mathis KB. Does total knee replacement restore normal knee function? *Clin Orthops Rel Res* 2005;413:157-65.
- 3 Shamley DR, Barker K, Simonite V, Beardshaw A. Delayed versus immediate exercises following surgery for breast cancer: a systematic review. *Breast Cancer Res Treat* 2005;90:263-71.
- 4 Knipschild P. Systematic reviews: some examples. *BMJ* 1994;309:719-21.
- 5 Main E. Advantages and limitations of systematic reviews in physical therapy. *Cardiopulm Phys Ther J* 2003;14:24-7.
- 6 Sultan PG, Schule S, Li G, Rubash HE. Optimizing flexion after total knee arthroplasty: advances in prosthetic design. *Clin Orthop Rel Res* 2003;416:167-73.

Accepted: 8 August 2007

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

Michael S Kramer,¹ Lidia Matush,² Irina Vanilovich,³ Robert Platt,⁴ Natalia Bogdanovich,³ Zinaida Sevkovskaya,³ Irina Dzikovich,³ Gyorgy Shishko,³ Bruce Mazer⁵

EDITORIAL by Gahagan

¹Departments of Pediatrics and of Epidemiology and Biostatistics, McGill University Faculty of Medicine; and Institute of Human Development and Child and Youth Health, Canadian Institutes of Health Research (CIHR), Montreal, Canada

²Maternal and Child Health Department, Belarussian Ministry of Health

³Belarussian Maternal and Child Health Research Institute

⁴Departments of Pediatrics and of Epidemiology and Biostatistics, McGill University; and IS/IT, McGill University Health Centre Research Institute, Montreal

⁵Department of Pediatrics, McGill University; and Division of Pediatric Allergy and Clinical Immunology, Montreal Children's Hospital, McGill University Health Centre

Correspondence to: M S Kramer, Montreal Children's Hospital, 2300 Tupper Street (Les Tourelles), Montreal, Quebec H3H 1P3 michael.kramer@mcgill.ca

BMJ 2007;335:815-8

doi:10.1136/bmj.39304.464016.AE

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 Belarussian 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.

Trial registration Current Controlled Trials ISRCTN37687716.

INTRODUCTION

Research findings indicating a beneficial effect of breast feeding on the development of allergy have been most consistent for atopic eczema during infancy, but the evidence on asthma and other atopic outcomes is mixed. Some studies have reported greater degrees of protection with more exclusive and prolonged breast feeding.¹⁻⁴ Other studies have reported no reduction in risk or even an increase in risk with breast feeding.⁵⁻¹²

Virtually all of the evidence is based on observational studies. Case-control studies are prone to recall bias. Cohort studies are prone to biased assessment of outcomes when observers are not blinded to the previous infant feeding history. Misclassification of infant feeding history is always a problem in studying the health effects of breast feeding but is even more problematic in studies of atopic disease, in which hypersensitivity reactions and atopic disease may not show dose-response effects and may be affected by the frequency and timing of breast feeding.

One solution to these methodological problems is a randomised controlled trial. Although randomising

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

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

ICC=intraclass correlation coefficient.
*For experimental group versus control group.

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.¹³ 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 Belarussian 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.¹⁴ 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.¹³

The two randomised groups were similar in baseline sociodemographic and clinical variables.¹³ 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%; $P = 0.01$).¹³

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.¹⁵ Paediatricians did skin prick tests to five antigens: house dust mite, cat, birch pollen, mixed northern grasses, and *Alternaria*. Because

blinding of paediatricians to the experimental versus control assignment was not feasible, we randomly selected five children per paediatrician for blinded audit, for a total of 190 audited children.

We based all statistical analyses on intention to treat. We analysed differences in outcome between the experimental and control groups by using a multilevel statistical modelling procedure that accounts for the clustered randomisation.¹⁶ The cluster adjusted differences presented in the text and tables are very similar to those obtained from a multivariate model that adjusts for stratum level variables (geographic region and urban versus rural location), as well as individual level covariates.

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 κ 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 $\geq 10\%$ 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).

Table 2 | Skin prick test results. Values are numbers (percentages) positive unless stated otherwise

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

ICC=intraclass correlation coefficient.

*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 χ^2 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 χ^2 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.

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

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

ICC=intraclass correlation coefficient.

*For experimental group versus 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.^{1-4 17-20} 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.⁷⁻¹² Some investigators have found stronger protective effects of breast feeding in offspring with a positive family history of atopy,^{17 18} 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.²¹ 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.¹³ 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.¹³

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.

MSK is a senior investigator of the Canadian Institutes of Health Research. RP is a Monat-McPherson career investigator of McGill University, and both he and BM are career investigators (chercheurs-boursiers) of the Fonds de la recherche en santé du Québec.

Contributors: See bmj.com.

Funding: Grant (MOP No 53155) from the Canadian Institutes of Health Research. The funder had no role in study design, data collection, data analysis, data interpretation, or writing of this manuscript.

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.

- 1 Saarin UM, Kajosaari M. Breastfeeding as prophylaxis against atopic disease: prospective follow-up study until 17 years old. *Lancet* 1995;346:1065-9.
- 2 Dell S, To T. Breastfeeding and asthma in young children. *Arch Pediatr Adolesc Med* 2001;155:1261-5.
- 3 Kull I, Almqvist C, Lilja G, Pershagen G, Wickman M. Breast-feeding reduces the risk of asthma during the first 4 years of life. *J Allergy Clin Immunol* 2004;114:755-60.
- 4 Rothenbacher D, Weyermann M, Beermann C, Brenner H. Breastfeeding, soluble CD14 concentration in breast milk and risk of atopic dermatitis and asthma in early childhood: birth cohort study. *Clin Exp Allergy* 2005;35:1014-21.
- 5 Stabell Benn C, Wohlfahrt J, Aaby P, Westergaard T, Benfeldt E, Michaelsen KF, et al. Breastfeeding and risk of atopic dermatitis, by parental history of allergy, during the first 18 months of life. *Am J Epidemiol* 2004;160:217-23.
- 6 Burgess SW, Dakin CJ, O'Callaghan MJ. Breastfeeding does not increase the risk of asthma at 14 years. *Pediatrics* 2006;117:787-92.
- 7 Taylor B, Wadsworth M, Wadsworth J, Peckham C. Changes in the reported prevalence of childhood eczema since the 1939-45 war. *Lancet* 1984;2:1255-7.
- 8 Takemura Y, Sakurai Y, Honjo S, Kusakari A, Hara T, Gibo M, et al. Relation between breastfeeding and the prevalence of asthma: the

- Tokorozawa childhood asthma and pollinosis study. *Am J Epidemiol* 2001;154:115-9.
- 9 Sears MR, Greene JM, Willan AR, Taylor DR, Flannery EM, Cowan JO, et al. Long-term relation between breastfeeding and development of atopy and asthma in children and young adults: a longitudinal study. *Lancet* 2002;360:901-7.
 - 10 Purvis DJ, Thompson JMD, Clark PM, Robinson E, Black PN, Wild CJ, et al. Risk factors for atopic dermatitis in New Zealand children at 3.5 years of age. *Br J Dermatol* 2005;152:742-9.
 - 11 Wegienka G, Ownby DR, Havstad S, Keoki Williams L, Cole Johnson C. Breastfeeding history and childhood allergic status in a prospective birth cohort. *Ann Allergy Asthma Immunol* 2006;97:78-83.
 - 12 Wright AL, Holberg CJ, Taussig LM, Martinez FD. Factors influencing the relation of infant feeding to asthma and recurrent wheeze in childhood. *Thorax* 2001;56:192-7.
 - 13 Kramer MS, Chalmers B, Hodnett ED, Sevkovskaya Z, Dzokovich I, Shapiro S, et al. Promotion of breastfeeding intervention trial (PROBIT): a randomized trial in the Republic of Belarus. *JAMA* 2001;285:413-20.
 - 14 WHO/UNICEF. *Protecting, promoting and supporting breastfeeding: the special role of maternity services*. Geneva: World Health Organization, 1989.
 - 15 Asher MI, Keil U, Anderson HR, Beasley R, Crane J, Martinez F, et al. International study of asthma and allergies in childhood (ISAAC): rationale and methods. *Eur Respir J* 1995;8:483-91.
 - 16 Breslow NE, Clayton DG. Approximate inference in generalized linear mixed models. *J Am Stat Assoc* 1993;88:9-25.
 - 17 Gdalevich M, Mimouni D, David M, Mimouni M. Breast-feeding and the onset of atopic dermatitis in childhood: a systematic review and meta-analysis of prospective studies. *J Am Acad Dermatol* 2001;45:520-7.
 - 18 Gdalevich M, Mimouni D, Mimouni M. Breast-feeding and the risk of bronchial asthma in childhood: a systematic review with meta-analysis of prospective studies. *J Pediatr* 2001;139:261-6.
 - 19 Mimouni Bloch A, Mimouni D, Mimouni M, Gdalevich M. Does breastfeeding protect against allergic rhinitis during childhood? A meta-analysis of prospective studies. *Acta Paediatr* 2002;91:275-9.
 - 20 Oddy WH, Holt PG, Sly PD, Read AW, Landau LI, Stanley FJ, et al. Association between breast feeding and asthma in 6 year old children: findings of a prospective birth cohort study. *BMJ* 1999;319:815-9.
 - 21 International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. *Lancet* 1998;351:1225-32.

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 shared by the interviewees, because they were scared of the large gecko that roamed around. They made constant 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.

Clint mentioned that the interviewees were very serious throughout the interviews, but at this question they would always look up and smile. "Who would rent my house?" they would ask.

Clint would insist, "I do, I want to rent your house. How much for?" He always got an answer out of them in the end.

Hannah Kuper lecturer in epidemiology, London School of Hygiene and Tropical Medicine, Londonhannah.kuper@lshtm.ac.uk

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.