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ORIGINAL ARTICLE

The effect of brief neonatal exposure to cows' milk on atopic symptoms up to age 5

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Aims: To determine the effect of brief early exposure to cows' milk on the expression of atopy during the first five years of life.

Methods: Follow up analysis of a double blind, placebo controlled, randomised feeding intervention trial (BOKAAL study). Subjects were 1108 children from 1533 initially randomised breast fed neonates in the Netherlands. Atopic disease and prevalence of allergic symptoms at age 1, 2, and 5, and specific IgE at age 1 and 5 were determined.

Results: Atopic disease in the first year was found in 10.0% (cows' milk) versus 9.3% (placebo) of the children, with a relative risk (RR) of 1.07. No differences were found in the second year either. At age 5, atopic disease was found in 26.3% (cows' milk) versus 25.0% (placebo), RR 1.05. There was no difference in the prevalence of allergic symptoms. Specific IgE to cows' milk (RAST positive 2+ or more) was 5.8% (cows' milk) versus 4.1% (placebo) at age 1 (RR 1.43), and 5.3% versus 3.0% at age 5 (RR 1.77). There was no difference in sensitisation to other common allergens between the two groups.

Conclusion: Early, brief exposure to cows' milk in breast fed children is not associated with atopic disease or allergic symptoms up to age 5.

Asthma, hay fever, eczema, and food allergy are common, serious health problems in children. The incidence of these atopic diseases has been increasing during the past century in the developed countries in the world.¹

Genetic and environmental factors are responsible for the predisposition and expression of allergic disorders.² Susceptibility to developing allergic asthma, hay fever, and eczema may be increased by factors present in early life. These include male gender, low birth weight, preterm birth, young maternal age, maternal smoking, and possibly, early cessation of exclusive breast feeding.³ In a birth cohort in Germany, socioeconomic factors, phenotype of the parents, and smoking were the most important factors for developing atopy.³

Development of the neonatal, physiologically immature immune system is critically influenced by environmental exposures in the early months of life, which therefore is an important period for sensitisation and later development of allergy. However, the duration of this period is not clear, and some environmental exposures may also be important for developing tolerance.

Environmental inhaled irritants and aeroallergens, passive smoking, respiratory viral infections early in life, and the season of birth may all influence sensitisation. Also, having older sibs and early attendance to day care centres may contribute to atopic sensitisation, the suggestion being that both of these increase exposure to infectious agents which may induce the immune system to develop away from an allergic response.⁵

The role of breast feeding and/or avoidance of cows' milk based formulae in early infancy has been the focus of much controversy. A clear association has been found between the diversity of the infant's diet during the first months of life and development of eczema. Saarinen and Kajosaari² concluded that breast feeding was prophylactic against atopic disease throughout childhood and adolescence, in a prospective follow up study until 17 years of age. Oddy and Holt³ conducted a prospective birth cohort study and found delayed introduction of milk other than breast milk until at least 4 months of age to be associated with a reduction in the risk of asthma and atopy at age 6, and with a significant delay in the age at onset of wheezing and doctor diagnosed asthma.

Whereas this literature suggests that breast feeding may reduce the incidence of allergic disease later in life, some investigators have suggested that brief, neonatal exposure to cows' milk formulae as frequently occurs in maternity wards, may increase the risk for developing atopic disease.^{6,7} To determine the effect of brief early exposure to cows' milk on the development of allergic symptoms, we initiated a placebo controlled intervention trial (the "BOKAAL" study). In this study, 1533 breast fed neonates randomly received intervention feeding during the first three days after birth—either a supplementary standard whey protein dominant cows' milk formula (Nutrilon Premium; Nutricia, Zoetermeer, Netherlands), or a placebo formula. Breast feeding was encouraged for at least six weeks. The children were followed up for two years. Results up to two years of follow up have been published previously.⁸ Briefly, there was no difference between the two groups in either atopic disease or sensitisation to common allergens. Obvious atopic disease in the first year was found in 73/730 children in the cows' milk group and in 70/752 children in the placebo group. The study was unblinded after the second year of follow up. Atopic disease in the first two years was mainly a result of eczema. Because two years was too short a study period to draw a conclusion about the risk or benefit towards asthma and atopic symptoms, and the long term effect of early and brief exposure to cows' milk is not known, we evaluated the BOKAAL cohort at age 5.

METHODS

Study population

The study population consisted of those children from the original BOKAAL study, the parents of whom had consented to being approached for follow up at age 5. The protocol for the study was approved by the Institutional Review Board of the Academic Medical Center of the University of Amsterdam, and written informed consent from the parents was again obtained

Abbreviations: RAST, radioallergosorbent test; RR, relative risk

Table 1 Characteristics of the study population

Characteristics at age 5 (n=1108)	Cows' milk (n=542)	Placebo (n=566)
Sex, % female	48.3	49.3
No siblings at age 5	7.0	6.2
Older siblings	52.8	49.3
Younger siblings	56.5	61.7
Family history of atopy: asthma or hay fever, assessed at age 5		
Maternal history (n=1107)	29.4	30.7
Paternal history (n=1091)	30.0	30.0
Both parents (n=1098)	8.9	9.3
At least one of the parents (n=1098)	50.7	51.3
Siblings history (n=1004)	19.3	21.4
At least one of the family members (n=1081)	56.4	58.0
Maternal education		
Low	26.1	27.4
Middle	41.9	41.0
High	32.0	31.6
Exclusive breast feeding period		
≤2 weeks	33.4	26.9
>2 but ≤5 weeks	14.8	14.8
>5 weeks but ≤3 months	22.5	27.0
>3 but ≤4 months	10.1	8.7
>4 but ≤6 months	10.9	14.5
≥6 months	8.3	8.1
Pets at home		
Exposure before birth	55.5	60.4
Exposure at age 1	51.8	58.0
Exposure at age 2	51.8	52.8
Exposure at age 5	49.4	50.9
Day care attendance until school age		
Exposure until age 1	24.9	24.7
Exposure age one until 2	17.9	17.5
Exposure age one until 3	20.7	20.2
Exposure age 2 until 3	19.9	21.2
Exposure age 3 until 4	19.9	19.5
Smoking in the household		
Exposure during pregnancy (maternal only)	17.5	16.8
Exposure at age 1	30.8	31.1
Exposure at age 2	32.9	32.1
Exposure at age 5	37.8	37.1

Results expressed as percentages.

for each child. A questionnaire was completed, assessing demographic variables, family characteristics and risk of atopy, indoor and outdoor risk factors such as pets and smoking, and an assessment of the current health status of the children and the medical history of the past years. All children (except for two living abroad) were seen by two investigators (MdJ and VS) and were examined for the presence of atopic eczema according to the ISAAC protocol,⁸ for (rhino)conjunctivitis, wheezing, and other clinical signs of allergy. A venous blood sample was taken for the assessment of specific IgE by radioallergosorbent test (RAST) against cows' milk, hen's egg, house dust mite (*Dermatophagoides pteronyssinus*), cat dander and dog dander, which were all tested at age 1; additionally grass pollen (a mix of *Phleum pratense* and *Dactylis glomerata*), tree pollen (a mix of birch, alder, hazel, and willow) and moulds (a mix of *Aspergillus fumigatus*, *Alternaria alternata*, *Cladosporium herbarum*, and *Penicillium notatum*) were tested. The results of the laboratory tests were expressed as negative (normal) or ranged from 1+ (dubious) to 5+ (strongly positive).

Outcome definitions

The primary outcome at age 5 was the presence of atopic disease according to the following categories: obvious, possible, and no atopic disease. We classified the children as having "obvious atopic disease" if any of the following symptoms occurred: (1) wheeze in the past year; (2) sneezing with

itchy-watery eyes in the past year; or (3) itchy rash in the past year with any flexural involvement (around the eyes, around the sides or front of the neck, fronts of the elbows, behind the knees, or on the fronts of the ankles). Children who fulfilled at least one of the following criteria were classified as having "possible atopic disease": (1) an affirmative answer to at least one of the questions: Has your child ever had asthma? Has your child ever had hay fever? Has your child ever had eczema?; (2) any flexural involvement ever, but no itchy rash in the past year; (3) itchy rash in the past year but no flexural involvement; (4) sneezing during April to September, but not accompanied by itchy-watery eyes; (5) a positive answer to the question: Is your child allergic for house dust, for pets, or for pollen? The remaining children were classified as having "no atopic disease".

For the prevalence measures the following core questions on asthma, allergy, and eczema of the International Study on Childhood Asthma and Allergy (ISAAC) were incorporated in the questionnaire.⁹

Wheeze at age 5 was defined as a positive answer to the question: Has your child had wheezing or whistling in the chest in the past 12 months? In addition, the questions: How many attacks of wheezing has your child had in the past 12 months? and How often, on average, has your child's sleep been disturbed because of wheezing in the past 12 months? were used to get insight in prevalence and severity.

Table 2 Clinical outcome at age 5 and the cumulative incidence of atopic diseases

Clinical outcome	Cows' milk (n=542)	Placebo (n=566)	OR (95% CI)	Adjusted OR (95% CI)*
Atopic disease at age 5				
Obvious	26.3 (142)	25.1 (142)	1.02 (0.77 to 1.35)†	0.99 (0.73 to 1.33)
Possible	20.0 (108)	22.6 (128)	0.86 (0.64 to 1.17)‡	0.83 (0.60 to 1.14)
No	53.7 (290)	52.3 (296)	Reference	
Wheeze in the past 12 months	11.5 (62)	10.4 (59)	1.11 (0.76 to 1.62)	1.07 (0.73 to 1.13)
Number of wheezing attacks in the past 12 months				
No attacks	89.4 (483)	90.1 (507)	Reference	
1–3 attacks	8.0 (43)	7.6 (41)	1.06 (0.75 to 1.51)§	
4–12 attacks	2.2 (12)	2.3 (13)	0.97 (0.47 to 2.00)¶	
More than 12 attacks	0.4 (2)	0.4 (2)		
Sleep disturbance due to wheezing, on average in the past 12 months				
Never woken with wheezing	93.1 (502)	94.1 (531)	Reference	
Less than one night per week	4.5 (24)	3.9 (22)	1.17 (0.75 to 1.85)**	
One or more nights per week	2.4 (13)	2.0 (11)		
Sneezing with itchy–watery eyes last year	4.1 (22)	6.0 (33)	0.67 (0.39 to 1.17)	0.62 (0.35 to 1.13)
Itchy rash last year	15.9 (86)	20.1 (114)	0.75 (0.55 to 1.03)	0.76 (0.55 to 1.04)
Flexural dermatitis at examination (n=1055)	9.0 (47)	9.0 (48)	1.01 (0.66 to 1.54)	0.95 (0.61 to 1.47)
Cumulative incidence of atopic disease (n=1108)	31.5 (171)	29.5 (167)	1.05 (0.79 to 1.40)	1.00 (0.74 to 1.36)

*Adjusted for: family risk of atopy, gender, siblings, smoking during pregnancy, smoking in the house hold at age 1, day care attendance at age 1, furred pets at age 1, duration of breast feeding, having older sibs, introduction of solid foods before 5 months.

†Obvious versus no; ‡possible versus no.

§No attacks versus having attacks in the last year; ¶0–3 attacks versus having 4 or more attacks in the past year.

**Never awake versus awake due to wheezing in the past year.

Sneezing with itchy–watery eyes, as an indicator for hay fever, was defined as an affirmative answer to the following two questions: In the past 12 months, has your child had a problem with sneezing or a runny or blocked nose when he/she did not have a cold or the flu? In the past 12 months, has this nose problem been accompanied by itchy–watery eyes?

Eczema was defined as a positive response to the question: Has your child had an itchy rash in the past 12 months? To gain insight in the severity of symptoms, we received categorical answers to the question: In the past 12 months, on average, has your child been kept awake at night by this itchy rash? Flexural dermatitis was defined as the presence of dermatitis at physical examination on at least one of the following five areas: around the eyes, around the sides or front of the neck, fronts of the elbows, behind the knees, or on the fronts of the ankles.

We defined a positive family history for atopy at age 5 if at least one of the parents reported to have ever suffered from asthma or hay fever (ISAAC questionnaire). Before birth of the child and at age 1 we included questions about shortness of breath in several circumstances and affirmative answers on sensitisation to house dust mite, pets, and pollen. We excluded questions on eczema from the definition of family history, as earlier experience showed that eczema in an adult population was very poorly associated with sensitisation.¹⁰ Siblings were excluded from the definition of family risk of atopy to make the association more pure. Maternal smoking during pregnancy was assessed separately from exposure to environmental tobacco smoke after birth, defined by the presence of any smoking inside the home. For exposure to pets, we included all pets during the first years and only furred pets kept inside the home at age 5.

Maternal education was used as a measure for socioeconomic status, in three categories of increasing educational achievement.

Sensitisation at age 5 was defined by any of the eight above mentioned RASTs being clearly positive (2+ or more).

We also combined the results of the clinical and laboratory assessments at age 5 by classifying children into three groups, as at age 1: (1) obvious atopy was defined as obvious atopic

disease, regardless of the sensitisation by RAST, or as possible atopic disease with any positive RAST outcome; (2) possible atopy was defined as possible atopic disease without any positive RAST outcome, or as no atopic disease with any RAST positive outcome; (3) no atopy was defined as both negative clinical and negative laboratory outcome.

The cumulative incidence of atopic disease was analysed as the most severe clinical outcome at age 1, 2, or 5.

Data were analysed using SPSS 9. We calculated simple odds ratios (OR) or relative risks (RR) with corresponding 95% confidence intervals (CI) from cross tabulations. Multivariate analyses, adjusting for confounding factors, were conducted with binary logistic regression.

RESULTS

The BOKAAL study has a high response rate. About 90% of mothers asked by the midwives before birth agreed to participate (n = 1693). After birth, 160 children were not randomised (see de Jong and colleagues⁸ for reasons for exclusion). The drop outs occurred mostly during the second year, mainly because of logistic circumstances, and were equally distributed over the intervention groups. We analysed baseline characteristics and outcome at age 1 and 2 for responders and non-responders at age 5 and found no statistical differences, although the responders tended to have somewhat higher educated mothers who smoked less during pregnancy.

From 1992 to 1994, 1533 children were randomised for the first part of the BOKAAL study. At age 2, 1180 parents (in 1220 fulfilled questionnaires) agreed to follow up at age 5. Eventually, 1108 children (72.2% of the original cohort) participated in this second part of the study by questionnaire, 1058 of them underwent a physical examination, and a venous blood sample was taken from 943 children. As shown in table 1, no substantial differences were found in the baseline characteristics of the study population between the intervention groups. Mean age at physical examination was 5 years 10 months (range 5.5–7.5 years).

Obvious atopic disease was found in 26.3% of the children exposed to cows' milk and in 25% of the placebo exposed children. The relative risk was 1.05 (95% CI 0.86 to 1.29).

Table 3 Specific IgE 2+ and more in relation to the intervention and the combination of clinical outcome with specific IgE at age 5

Specific IgE, measured by RAST at age 5	Cows' milk (n=472)	Placebo (n=468)	Relative risk (95% CI)
Any RAST (n=934)	17.3 (82/467)	17.7 (83/467)	0.99 (0.75 to 1.30)
Cows' milk	5.3 (25/470)	3.0 (14/467)	1.77 (0.93 to 3.37)
Hen's egg	0.2 (1/470)	0.6 (3/467)	0.33 (0.04 to 3.17)
House dust mite	9.3 (44/470)	9.2 (43/467)	1.02 (0.68 to 1.51)
Cat dander	2.1 (10/471)	3.4 (16/468)	0.62 (0.29 to 1.35)
Dog dander	1.1 (5/472)	1.7 (8/467)	0.62 (0.20 to 1.88)
Grass pollen	5.6 (26/467)	7.5 (35/466)	0.74 (0.45 to 1.21)
Tree pollen	3.2 (15/467)	3.0 (14/466)	1.07 (0.52 to 2.20)
Moulds	1.1 (5/466)	1.3 (6/467)	0.84 (0.26 to 2.72)
Combined outcome, atopy (n=932)			
Obvious (n=281)	31.6 (147/465)	28.7 (134/467)	1.05 (0.87 to 1.26)*
Possible (n=210)	20.6 (96/465)	24.4 (114/467)	0.88 (0.71 to 1.10)†
No (n=441)	47.7 (222/465)	46.9 (219/467)	Reference

*Obvious versus no; †possible versus no.

Wheezing during the past 12 months at age 5 was reported for 62 children (11.5%) in the cows' milk intervention group (n = 541) and in 58 (10.3%) of the placebo group (n = 564). The associated odds ratio was 1.11 (95% CI 0.76 to 1.62). Furthermore, all the other analysed clinical outcome measures showed no differences between the cows' milk and placebo groups (table 2). When adjusted for duration of exclusive breast feeding, sex, parental history of atopy, smoking during pregnancy and smoking in the household at age 1, having older sibs, day care attendance at age 1, the introduction of solid foods before the age of 5 months, and pets at age 1, no substantial differences were found.

At age 1, we found 9.4% children in the cows' milk group positive for any RAST (2+ or more) versus 7.9% in the placebo group. At age 5, these figures were 17.3% versus 17.7%. As was to be expected, positivity for hen's egg was less frequent at age 5 than at age 1, while positivity for aeroallergens was much more frequent, mainly house dust mite and grass pollen (table 3). Sensitisation to cows' milk was found in 5.8% in the cows' milk group versus 3.0% in the placebo group, with a relative risk of 1.77 (95% CI 0.93 to 3.37).

A per protocol analysis was performed for all children who received at least three times the randomised supplementation of cows' milk or placebo (intervention feeding) and at least six weeks exclusively breast feeding (table 4). Again we found no differences between the intervention groups.

Parental history of atopy was assessed before birth and at age 5. The proportion of positive parental risk at birth (in the remaining group at age 5) was 37.6%, and 51% assessed at age 5 (560 children). This shows that parents of 181 children switched from negative at birth to positive at age 5. However,

in this "switch group" there was no association with the outcome of obvious atopic disease at age 5 in a trend analysis, neither in the negative parental history group (Mantel-Haentzel with 1 df, value = 2.298, p = 0.13), nor in the positive group (Mantel-Haentzel with 1 df, value = 1.108, p = 0.29).

DISCUSSION

This study indicates that breast fed children who received cows' milk supplementation during the first three days of life showed the same risk of clinical or serological expression of atopic disease at age 5 as those who received a placebo formula. Again, the "dangerous bottle" concept could not be confirmed in our study group.⁶ It is unlikely that the amount of cows' milk was not sufficient to sensitise the children. As reported earlier, the mean volume of formula feeding in our study (120 ml) was considerably more than the estimated minimum amount required to induce sensitisation. No differences were found by Gustafsson *et al*, who reported a cumulative incidence of atopic disease in Swedish children at 7 and 11 years who received supplementary human donor milk or a cows' milk based formula in maternity wards.¹¹ Neither could they find a relation between the dose of cows' milk formula and the subsequent incidence of atopic disease, despite literature suggesting that small doses of foreign proteins may be more likely to provoke sensitisation than larger ones.¹²

Saarinen *et al* found, in her prospective study, that supplementation with cows' milk in maternity hospitals increased the risk of cows' milk allergy at 18 months, just like

Table 4 Per protocol analysis: clinical outcome and cumulative incidences of atopic diseases for all children who received at least three intervention feeds and exclusive breast feeding for at least six weeks

Clinical outcome	Cows' milk (n=271)	Placebo (n=311)	OR (95% CI)	Adjusted OR (95% CI)*
Atopic disease at age 5 (n=582)				
Obvious	24.4 (66)	26.4 (82)	0.85 (0.58 to 1.29)†	0.84 (0.55 to 1.28)
Possible	21.8 (59)	23.8 (74)	0.83 (0.55 to 1.26)‡	0.83 (0.54 to 1.28)
No	53.9 (146)	49.8 (155)	Reference	
Wheeze in the past 12 months (n=586)	8.5 (23)	9.5 (30)	0.86 (0.49 to 1.53)	0.93 (0.52 to 1.69)
Sneezing with itchy-watery eyes last year (n=570)	3.8 (10)	5.9 (18)	0.62 (0.28 to 1.37)	0.63 (0.27 to 1.48)
Itchy rash last year (n=586)	17.8 (48)	22.2 (70)	0.74 (0.49 to 1.12)	0.74 (0.48 to 1.14)
Flexural dermatitis at examination (n=565)	9.2 (24)	9.2 (28)	1.00 (0.56 to 1.76)	0.96 (0.53 to 1.75)
Cumulative incidence of atopic disease (n=587)	29.9 (81)	30.1 (95)	0.97 (0.65 to 1.44)	0.93 (0.61 to 1.42)

*Adjusted for: family risk of atopy, gender, having older sibs, smoking in the household, day care attendance, furred pets, duration of breast feeding.

†Obvious versus no; ‡possible versus no.

obvious parental atopy, in comparison with feeding of other supplements. Exclusive breast feeding did not eliminate the risk.⁷

As Hånson expressed, the positive effects of breast feeding are beyond dispute, as immunomodulatory, anti-inflammatory, nutritional, and other components are provided in human milk.¹³

We previously reported the outcome at age 1 and 2 and found no differences between the intervention groups regarding atopic dermatitis and gastrointestinal disease caused by food allergy. Now, at age 5, the incidence of atopic disease increased in both groups to over 25%, mainly because of wheeze and eczema. With regard to our whole cohort, 9% of the children at age 5 still showed flexural dermatitis at physical examination and 18% reported itchy rash in the past year. This is considerably more than the 9.6% prevalence of itchy rash Wieringa *et al* found in a cross sectional study in 6–7 year old Belgian children.¹⁴ It is also higher than the 13.5% flexural dermatitis found in Dutch school children, although in that group, as in our study, 25% also reported one or more atopic symptoms.¹⁵

However, our data indicate that if there is any effect of brief neonatal exposure to cows' milk, the effect is not as harmful as might be thought, even in high risk children, who are exposed to many risk factors.

Conclusion

Early and brief exposure to cows' milk in breast fed children is not associated with atopic disease or allergic symptoms up to age 5.

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ARCHIVIST

Propranolol after severe burns

After severe burns there is an initial phase of hypoperfusion followed by a postinjury response of fever, hyperdynamic circulation, and protein catabolism. Muscle proteolysis continues for 9 months or more. The underlying mechanisms are complex and multifactorial but include increased secretion of catecholamines. Management includes supplemental nutrition, maintenance of hydration, mechanical ventilation as necessary, pain control, and early wound excision and closure. Now researchers in Texas (David N Herndon and colleagues. *New England Journal of Medicine* 2001;**345**:1223–9; see also editorial, *ibid*: 1271–2) have shown that treatment with propranolol reduces hypermetabolism and reverses muscle breakdown.

Twenty-five children (mean age 7 years) with severe burns (> 40% of body surface area) were randomised to propranolol via nasogastric tube (dose adjusted to achieve 20% fall in heart rate; average eventual dose 1.05 mg/kg every 4 hours) or no propranolol, beginning about 2 weeks after injury. In the next 4 weeks the decrease in heart rate and resting energy expenditure was significantly greater in the propranolol group. Muscle protein balance was assessed from the rate of incorporation of labelled phenylalanine, in sequential muscle biopsies and increased by 82% over baseline values in the propranolol group but decreased by 27% in the control group. Fat-free mass, measured by whole-body potassium scanning, stayed constant in the treated group but fell by a mean of 9% in the control group.

Long term treatment with a beta blocker may benefit severely burned children by reversing muscle protein catabolism.