

A low allergen diet is a significant intervention in infantile colic: Results of a community-based study

David J. Hill, FRACP,^a Irene L. Hudson, PhD,^b

Leslie J. Sheffield, FRACP, MSc,^c Michael J. Shelton, PhD,^a

Samuel Menahem, MD, FRACP,^a and Clifford S. Hosking, MD, FRACP^a

Melbourne, Australia

Background: The effect of diet change in 38 bottle-fed and 77 breast-fed "colicky" infants, referred from community-based pediatric facilities was studied over a 1-week period in a double-blind (within each feeding mode), randomized, placebo-controlled trial.

Methods: Bottle-fed infants were assigned to either casein hydrolysate or cow's milk formula. All mothers of breast-fed infants were started on an artificial color-free, preservative-free, additive-free diet and also randomized to an active low allergen diet (milk-, egg-, wheat-, nut-free) or a control diet.

Results: The response to diet was assessed on day 1 and day 8 with the use of a previously validated infant distress chart on which parents recorded distress levels. If successful outcome was defined as a reduction in distress of 25% or more, after adjusting for age and feeding mode, infants on active diet had a significantly higher rate of improvement than those on the control diet (odds ratio, 2.32; 95% confidence interval, 1.07-5.0; $p = 0.03$). Analysis of the day 8 to day 1 distress ratio, again adjusted for age and feeding mode, showed that infants on the active diet had distress reduced by 39% (95% confidence interval, 26-50) compared with 16% (95% confidence interval, 0-30) for those on the control diet ($p = 0.012$).

Conclusion: The results suggest a period of dietary modification with a low allergen diet and appropriate nutritional support should be considered in healthy infants with colic. (*J ALLERGY CLIN IMMUNOL* 1995;96:886-92.)

Key words: Infantile colic, food protein intolerance, dietary change

Infantile colic (i.e., unexplained paroxysms of crying or fussing) affects between 15% and 40% of infants in the first 4 months of life.¹⁻³ It is worse in the first 6 weeks of life, but then spontaneous improvement begins.⁴ The role of dietary factors in colic is controversial.⁵

Jacobsson and Lindberg⁶ reported that 53% of breast-fed infants experienced symptomatic improvement when cow's milk protein was excluded

Abbreviations used

CI:	Confidence interval
LR:	Logistic regression
MANOVA:	Multivariate analysis of variance
OR:	Odds ratio

from the maternal diet, but the significance of these findings was questioned because of the study design.⁷ Evans et al.⁸ could not confirm the findings of Jacobsson and Lindberg⁶ but noted a positive association between the number of food types in the maternal diet and severity of colic. Lothe et al.^{9, 10} reported the benefit of cow's milk protein exclusion with regard to colic in bottle-fed infants, but Forsyth,¹¹ in a crossover study, observed that this benefit was only transient. Half of the infants in one study by Lothe et al.⁹ had classical features of allergy to cow's milk and other

From ^aRoyal Children's Hospital, Melbourne; ^bDepartment of Statistics, University of Melbourne; and ^cMurdoch Institute for Research into Birth Defects, Melbourne.

Supported by a grant from Mead Johnson Nutritionals, International Division of Bristol-Myers Squibb Company, USA. Received for publication Nov. 15, 1994; revised Feb. 14, 1995; accepted for publication Feb. 14, 1995.

Reprint requests: David J. Hill, FRACP, Director, Department of Allergy, Royal Children's Hospital, Parkville 3052, Melbourne, Australia.

Copyright © 1995 by Mosby-Year Book, Inc.
0091-6749/95 \$5.00 + 0 1/1/64147

foods by the age of 6 months, suggesting that some of these patients initially had cow's milk allergy, of which colic is but one symptom.¹²

In this investigation the effect of dietary modification over a 1-week period on bottle-fed and breast-fed infants with colic was studied. Infants were randomly allocated to an active or control diet program. The study used a validated distress measurement tool,^{13, 14} was designed to be of sufficient duration to detect behavioral changes, and was performed in a randomized, double-blind, controlled manner, taking account of the mode of feeding, sex of the infant, and whether the infant was older or younger than 6 weeks of age. Because the study was designed to assess the effect of diet change, supportive contact between the research team and the subjects was discouraged until final assessments had been made.

The primary hypothesis to be tested was that the active diet would be more beneficial than the control diet; that is, this was a study of the efficacy of diet change in the treatment of colic. Secondary hypotheses, that the effect of diet would be different in different age or feeding mode strata, were also examined.

METHODS

Patients

Information regarding the study was distributed to pediatricians and community-based Maternal and Child Health nurses in the Melbourne metropolitan area. Infants with colic, who were otherwise healthy, were included if they were between the ages of 4 and 16 weeks, were the result of an uncomplicated pregnancy of more than 37 weeks' duration, and had an uneventful perinatal period.

Colic was defined as unexplained bouts of irritable and distressed behavior present for more than 3 hours per day, for more than 3 days per week, and of more than 3 weeks' duration.¹⁵ Infants with colic and a history of significant vomiting, diarrhea, eczema, persistent skin eruptions, or other symptoms suggestive of food protein intolerance or hypersensitivity were excluded from the study.^{12, 16-20} Patients receiving medication for treatment of colic continued receiving it throughout the study.

Conduct of study

Patients were assessed by one of two trained allergy research nurses who obtained informed consent and data, including age, sex, and feeding mode (breast or bottle) of the child. The research nurses issued parents with and instructed them in the use of a 24-hour distress score chart,¹³ which mothers were asked to complete, beginning on the morning after the first interview (day 1) and on the final day (day 8).

Infants were randomly allocated to the active or

control diet. The maternal diet or infant formula continued unchanged during the first 24 hours to document baseline behavior from 6:00 AM on day 1. On day 2 the diet program commenced and continued until review on day 9. The distress charts were scored by an independent "blinded" assessor. The study was approved by the Royal Children's Hospital Ethics Committee.

Diet programs

Breast-fed babies. All mothers who were breast-feeding were given a diet that excluded food dyes, additives, and preservatives. The active diet was oligo-antigenic. The following foods were allowed in the diet: rice, buckwheat, apple, pear, water, weak tea, weak coffee, potato, pumpkin, zucchini, marrow, lettuce, carrot, cauliflower, squash, lamb, beef, chicken, veal, turkey, fish, milk-free margarine, safflower oil, honey, sugar, salt, and pepper; all other foods were to be avoided. The control diet ensured a normal intake of cow's milk, meat, egg, wheat, nuts, and a wide range of fruits and vegetables. Suggested menus and instructions regarding the quantity of food required to ensure adequate nutrition were included on the diet sheets.

Bottle-fed babies. The infants in the *active* diet group received a hypoallergenic casein hydrolysate preparation (Pregestimil; Mead Johnson); infants in the *control* group received a modified cow's milk preparation (Enfalac Reduced Iron; Mead Johnson).

Study design

Infants were randomly allocated to the active or control diets within the strata defined by sex, feeding mode, and age. Treatment allocation was balanced for every four infants in the strata.

The study was double-blind and placebo-controlled in that formulas were dispensed in identical sealed tins (bottle-fed), diets were dispensed in sealed envelopes (breast-fed), and neither the participant nor the assessor was aware of the type of diet allocated to the patients.

Although the formulas had different tastes and the maternal diets had different levels of restriction, it is unlikely that the study was "unblinded" by the parents because patients were drawn from a wide geographic area, over a long period of time, and had no planned contact with each other. We are unaware of any unplanned contact, which could have allowed comparison of diets.

Sample size calculations

On the basis of previous studies of breast-fed infants with colic, a 20% spontaneous remission rate and a 50% rate of response to the active diet program was estimated;⁶ a sample size of 36 infants in each group was required ($\alpha = 0.05$, $\beta = 0.2$). For the bottle-fed infants, a similar spontaneous remission rate was used, and the response rate to diet was expected to be 60%^{9, 10}; thus, 20 bottle-fed infants were required to be in the active and control diets ($\alpha = 0.05$, $\beta = 0.2$).

Criteria for response to diet

As a *primary* outcome, "total distress levels" in minutes per 24 hours on day 1 and day 8 were measured from the distress score charts. The total distress levels were the sum of the duration of: (1) negative vocalizations (crying) and (2) fussing (agitated motor behavior) recorded on the distress score charts. A correlation between total distress levels and audiotaped duration of distress has been demonstrated.¹³ This total distress score has been used to distinguish infants with colic from infants without colic.¹⁴

Two criteria used to assess the primary outcome of the study were: (1) the incidence of reduction in total distress of more than 25% in the active and control diet groups, a level of improvement previously used to measure the result of interventions,^{21,22} and (2) a comparison of distress ratios day 8 to day 1 between infants on the active and control diets.

The *secondary* outcome measure was based on the maternal assessment. On day 9, mothers were asked whether they believed distressed behavior occurred less frequently on day 8 than on day 1. This assessment was undertaken to determine whether changes in distress scores were associated with benefits that could be perceived at a clinical level.

Analytical methods

Primary outcome: Reduction in distress of more than 25%. Categorical variables were analyzed by chi square, and odds ratios (ORs) and confidence intervals (CIs) were calculated.²³ Adjustment for confounding factors was made by logistic regression (LR).²⁴ Main effects of all stratifiers and their interactions with diet were entered into the LR model. The results were reported as ORs, 95% CIs, and associated *p* values.

Comparison of distress ratios. The ratio of day 8 to day 1 distress for the active and control diet groups was analyzed by tabulating the median values and calculating the Mann-Whitney U test and Fisher's exact test.²³ A multivariate analysis of variance (MANOVA) of the log-transformed ratio tested for a possible differential effect of diet according to the sex, age, and feeding mode of the infant. These stratifying variables were entered into the MANOVA model as single main effects and two- and three-way interaction with diet. Results were reported as predicted proportional changes, 95% CIs, and associated *p* values.^{25,26}

Secondary outcome. Infants were classified according to whether or not their mothers believed colic was less frequent on day 8 than on day 1.

Statistical computation of MANOVA and LR analysis were performed with the GLIM 3.77 package (Numerical Algorithms Group, Oxford, U.K.).²⁷ Outlier detection was performed with leverage and residual analysis.^{28,29} Initial and post hoc power analyses were performed according to the methods of Pocock²⁵ and Donner.²⁶ Statistical significance was achieved at a *p* value of less than 0.05, and all tests were two-sided.

RESULTS

At the outset, the study was expected to be completed within 12 months, but as it progressed, many sources of referral commenced implementation of the diet modification being tested by this research study, and patient referral ceased. Therefore after 3 years, the study was terminated, although the proposed number of bottle-fed infants had not reached the sample size sought. Thirty-six infants did not complete the second assessment, and after exclusion of this group, 122 infants remained. Fifty-four infants received the active diet, 67 received the control diet, and one was incorrectly allocated. Thirty-eight infants were bottle-fed, 77 were breast-fed, and seven were fed with both modes. Thirty-four were younger than 6 weeks of age, and 87 were older than 6 weeks of age. All mothers who attended the 1-week follow-up reported compliance with their allocated diet.

Because there was an insufficient number of infants in the mixed feeding mode group (*n* = 7) to allow analysis, this group was omitted, leaving 115 sets of results.

Table I shows the demographic features of the study and dropout groups. Chi square analysis and *t* tests showed no significant difference in these features between the groups. Of the 36 dropouts, 12 were younger than 6 weeks of age, and 24 were older than 6 weeks of age; 16 were bottle-fed (8 active, 4 control, 4 data incomplete), and 17 were breast-fed (8 control, 8 active, 1 data incomplete); the remaining three patients had incomplete feeding mode data recorded.

For the cohort of 115 infants, the mean age of the 54 patients assigned to the active diet was 7.0 weeks, and the mean age of those assigned to the control diet was 7.9 weeks. The mean day 1 total distress score for the active diet group was 330.5 minutes, and for the control diet group, 268.0 minutes (*p* = 0.12).

Primary outcome: Reduction in distress of more than 25%. Of the 115 infants, 61% on active diet (33 of 54) improved compared with 43% of those on the control diet (26 of 61) (OR, 2.12; 95% CI, 1.00-4.46; *p* = 0.047) (Table II).

The possible differential effect of diet depending on whether the infants were younger or older than 6 weeks of age, bottle-fed or breast-fed, and male or female, was examined, and each factor was adjusted by LR analysis. The effects of gender were not significant and are not reported.

Irrespective of diet and feeding mode, 46 of 81 infants (57%) older than 6 weeks of age

TABLE I. Demographic and clinical features of study groups

Variable	Group		
	Active	Control	Dropout
No. of cases	54	61	36
First child	26 (48%)	33 (54%)	21 (58%)
Second child	21 (39%)	16 (26%)	9 (25%)
Mother's age (yr)	29.1 + 4.3	29.4 + 3.8	28.6 + 4.2
Mother: Australian born	44 (81%)	48 (79%)	26 (72%)
Mother's education (yr)	13.6 + 2.8	13.2 + 2.4	13.3 + 3.5
Mother: On Social Security	5 (9%)	4 (7%)	3 (8%)
Single mother	3 (6%)	4 (7%)	1 (3%)
Father's age (yr)	31.1 + 6.1	31.7 + 5.0	30.8 + 4.7
Father: Australian born	45 (83%)	43 (70%)	26 (72%)
Father's education (yr)	14.1 + 4.0	13.2 + 4.2	13.5 + 2.7
Father: On Social Security	3 (6%)	3 (6%)	1 (3%)
Residence owned	39	51	28
Colic data			
Mean age at onset (wk)	2.2 + 1.7	2.0 + 1.7	2.4 + 2.6
Duration (wk)	5.1 + 3.0	5.9 + 3.1	4.7 + 2.9
Prior colic medication	46 (83%)	56 (92%)	32 (89%)
Seen Dr. more than once in past	23 (43%)	34 (56%)	17 (47%)
Current colic medication	33 (61%)	46 (75%)	24 (67%)
Previous diet changes	33 (61%)	38 (62%)	19 (53%)

Data are expressed as absolute numbers with percentages in parentheses or as mean + 1 SD.

improved compared with 13 of 34 infants (38%) younger than 6 weeks of age (OR, 2.12; 95% CI, 0.87-5.23; $p = 0.07$). Of the 34 infants younger than 6 weeks of age, 9 of 18 (50%) on the active diet and 4 of 16 (25%) on the control diet improved (OR, 3.0; 95% CI, 0.57-17.37; $p = 0.13$). Of the 81 infants older than 6 weeks of age, 24 of 36 (67%) on the active diet and 24 of 45 (49%) on the control diet improved (OR, 2.09; 95% CI, 0.77-5.74; $p = 0.10$). The LR model showed that age (i.e., <6 weeks and >6 weeks old) was a significant factor in determining improvement (OR, 2.36; 95% CI, 1.01-5.5; $p = 0.047$).

Improvement was analyzed according to whether the infants were breast-fed or bottle-fed. Overall, 38 of 77 (49%) breast-fed infants improved compared with 21 of 38 (55%) bottle-fed infants, irrespective of whether they received the active or control diet program (OR, 1.27; 95% CI, 0.54-2.98; $p = \text{NS}$). LR showed no significant effect of feeding mode on colic improvement.

The LR model prediction for infants younger than 6 weeks of age was 47% improved on active diet compared with 28% on the control diet. For infants older than 6 weeks of age, the prediction was 68% improved on the active diet compared with 48% on the control diet. After adjustment for age and feeding mode, infants on the active diet had a significantly

TABLE II. Effects of diet on colic improvement

	Clinical outcome		Statistics OR (95% CI)
	Improved*	Not improved*	
Overall outcome			
Active diet	33	21	2.12 (1.00-4.46)
Control diet	26	35	$p = 0.047$
Final outcome†			2.32 (1.07-5.0)
			$p = 0.03$

*Improved indicates a fall of more than 25% in distress score between day 1 and day 8; not improved indicates less change in distress scores between day 1 and day 8.

†Outcome after logistic model adjusted for effect of age (> or <6 weeks) on colic (see text).

higher rate of improvement than those on the control diet (OR, 2.32; 95% CI, 1.07-5.0; $p = 0.03$).

Comparison of distress ratios. For the total 54 patients on active diet, the median (day 8 to day 1) ratio was 0.70, a reduction of 90 min/24 hr, compared with 0.87, a reduction of 37 min/24 hr, for 61 infants on the control diet ($p = 0.09$).

The effect of diet change for the 115 infants was examined in each age group (<6 weeks or >6 weeks) and feeding mode stratum (breast-fed or

TABLE III. Overall effect of diet on colic distress ratio after adjustment for age and feeding mode

Diet	Predicted mean distress ratio*	Improvement† (%)	95% CI predicted improvement (%)	p Value‡
Active	0.61	39	26-50	0.012
Control	0.84	16	0-30	

*Adjusted (day 8 to day 1) distress ratio; adjusted for age and feeding mode.

†Change in distress over baseline (as percent), i.e., (Day 8-Day 1)/Day 1 based on adjusted means: adjusted for age and feeding mode.

‡As determined by MANOVA.

bottle-fed). An initial analysis performed on the subgroups showed a highly significant difference in the change in distress ratios between active and control diet for the breast-fed infants younger than 6 weeks of age ($p = 0.006$). No other effect of diet on the other subgroups was noted. To provide an overall analysis of all the subgroups, a MANOVA was used.

A preliminary MANOVA identified three bottle-fed infants with extreme values for their mean distress ratios with large residuals and leverage; two had distress reduced by more than 85% (1 on active diet, 1 on control diet) and one had distress increased by 295% (control diet). These outliers were omitted from the MANOVA in order to comply with the model's assumptions.

The MANOVA on the data from the remaining 112 patients showed that after correcting for feeding mode ($p = 0.059$) and age ($p = 0.013$), the mean day 8 to day 1 ratio was 0.61 for the 52 infants on active diet compared with 0.84 for the 60 infants on the control diet ($p = 0.012$) (Table III). These changes correspond to a reduction in distress time of 39% (95% CI, 26-50) for the active diet (a reduction of 117 min/24 hr), and 16% (95% CI, 0-30) for the control diet (a reduction of 46 min/24 hr).

No significant differential effect of diet according to age, feeding mode, or sex was found by testing two-way or three-way interactions in the MANOVA model. These results appeared to conflict with the above-mentioned data, which showed a marked effect of diet on breast-fed infants younger than 6 weeks of age; the breast-fed infants younger than 6 weeks of age on the control diet had distress *increased* by 34% (67 min/24 hr), whereas those on the active diet had distress *reduced* by 24% (73 min/24 hr). However, a post hoc power analysis on the data from all the pa-

tients showed there were insufficient numbers to detect interaction between age and feeding mode (Appendix).

Secondary outcome. Overall, 49 of 115 mothers reported that infant colic was improved by the end of the study. Forty-eight percent (26 of 54) of infants assigned to an active diet were rated as improved by the mother, compared with 38% (23 of 61) of those on the control diet (OR, 1.53, 95% CI, 0.73-3.23; $p = \text{NS}$).

DISCUSSION

According to the results of this study, diet is one factor that contributes to infant distress in the colic syndrome. This study was designed to investigate the effect of diet change on distressed behavior in infants in a community setting while minimizing the potentially confounding effects of counseling and support. The lack of supportive contact between the research team and patients may have contributed to the high dropout rate. Because the patients were receiving anticolonic medication and had previously been treated with diet modifications, these infants were probably at the more intractable end of the colic scale.

After correction for age and feeding mode, significantly more infants had distress reduced by 25% or more if they were on the active diet compared with the control diet ($p = 0.03$). The ratio of distress day 8 to day 1, again corrected for age and feeding mode, showed that the infants on the active diet had reduced median distress scores by 117 minutes compared with 46 minutes for those on the control diet ($p = 0.012$). These results were achieved in a double-blind study with a consecutive cohort of patients, whose contact was restricted to the study period, irrespective of previous use of anticolonic medications, dietary manipulation, or presence of psychosocial factors likely

to contribute to colic.³⁰ The findings have general applicability because infants were not hospitalized but referred by community-based pediatricians, family practitioners, and child health practitioners; and they had distress times comparable with infants in other investigations of diet^{10, 12, 31} and behavior intervention strategies^{22, 31} in colic.

Relevant to the secondary hypothesis, the greatest difference in the response to the diet was seen in the breast-fed infants younger than 6 weeks old in whom the *decrease* in distress for the active diet group contrasted with the *increase* in distress for the control group. This benefit of the active diet may have been accentuated because the natural history of colic is to deteriorate during the first 6 weeks of life.¹² The number of bottle-fed infants under the age of 6 weeks was too small to show a significant differential effect between active and control diets. In the infants 6 weeks of age and older, all groups recorded a *reduction* in distress, which was greater, but not significantly so, for the active diet group. Whether this improvement in distress in the control group represents the natural history of colic or the natural history combined with a placebo effect is a moot point. However, if the improvement in distress was due to a control effect, it was not seen among the infants younger than 6 weeks of age in whom the distress of the placebo-treated group increased. Whatever the basis for improvement in distress after 6 weeks of age, the proportion of the infants able to respond to diet change decreases, as does the statistical power to detect such a response.

There was no difference in the response to diet change between bottle-fed and breast-fed infants in that 57% of breast-fed infants, and 65% of bottle-fed infants assigned to an active diet had distress reduced by more than 25%. These rates of improvement are similar to Swedish studies, which have reported the benefit of cow's milk exclusion in breast-fed and bottle-fed infants.^{6, 19} However, our "active" diet for breast-feeding mothers not only excluded cow's milk but also restricted other common food allergens, which may have added to the benefit of the active diet.⁸ That 38% of breast-fed infants and 50% of bottle-fed infants assigned to the control diet program improved highlights the frequency with which spontaneous improvement of colic occurs.

The apparent benefits of diet for the whole study group need to be tempered with the following limitations of the study. First, not all subgroups showed a benefit of the diet; however, a post hoc power analysis demonstrated that only one subgroup, breast-fed infants older than 6 weeks of age,

had sufficient numbers to adequately test our secondary hypothesis. Thus the subgroup results should be cautiously interpreted. Second, the analysis was restricted to patients who completed the study and excluded dropouts; a more conservative analysis according to intention to treat, including dropouts classified as not improved, showed 47% of those on active diet improved compared with 36% of those on the control diet (OR, 1.61; 95% CI, 0.78-3.34; $p = 0.16$). Third, the maternal assessment did not show a significant benefit of the active diet over the control diet, although a positive association between reduction of distress and maternal assessment of this factor was demonstrated. However, the question asked of mothers could not discriminate different levels of improvement in colic, although 48% of mothers of infants on the active diet reported improvement compared with 38% of mothers of those on the control diet. Finally, the study was not of crossover design; such a design introduces further complexity because the period for crossover and washout required to induce remission and relapse of colic symptoms caused by adverse food protein reactions varies among patients and may take up to a week, depending on associated markers of immune hypersensitivity.^{12, 16, 18, 32, 33}

In this study colic has been used to describe healthy infants with distressed behavior and should not be assumed to denote a specific pathologic basis for this syndrome. Our findings suggest that diet is one factor that contributes to this entity. It is not clear whether this effect of diet is global or whether there is a subpopulation of distressed infants responsive to it, but the results suggest that in particular, breast-fed infants younger than 6 weeks of age may benefit from this intervention. Future investigations should focus on this younger age group. Possibly, some infants have colic because of transient protein intolerance,¹¹ which improves spontaneously from about 6 weeks of age,⁴ but distress may persist longer because of other factors, including disturbed parent-infant interaction.^{30, 31, 34, 35} A period of up to 2 weeks of dietary modification, with appropriate specialist nutritional support, should be considered in healthy infants with colic.

The secretarial assistance of Mrs. J. Sedmak is gratefully acknowledged. The clinical studies were conducted by Sisters A. Duke, SRN, and J. Brown, SRN. The diet programs were developed with the help of Mrs. B. Lynch, Dip.Inst.Man., Certif.Dietetics, MDAA, AO, formerly Chief Dietitian, RCH, Melbourne. Mr. Hok Pan Yuen of the Statistical Consulting Centre, University of Melbourne, assisted with data management.

REFERENCES

1. Hide DW, Guyer BM. The prevalence of infant colic. *Arch Dis Child* 1982;57:559-60.
2. Paradise JL. Maternal and other factors in the etiology of infantile colic. *JAMA* 1966;197:191-9.
3. Boulton TJC, Rowley MP. Nutritional studies during early childhood. III. Incidental observations of temperament, habits, and experiences of ill health. *Aust Paediatr J* 1979;15:87-90.
4. Brazelton TB. Crying in infancy. *Pediatrics* 1960;29:579-88.
5. Sampson HA. Infantile colic and food allergy: fact or fiction? *J Pediatr* 1989;115:583-4.
6. Jacobsson I, Lindberg T. Cow's milk proteins cause infantile colic in breast-fed infants: a double-blind crossover study. *Pediatrics* 1983;71:268-71.
7. Carey WB. Cow's milk formula and colic. *Pediatrics* 1984;84:1124-5.
8. Evans RW, Fergusson DM, Allardyce RA, et al. Maternal diet and infantile colic in breast-fed infants. *Lancet* 1981;1:1340-2.
9. Lothe L, Lindberg T, Jacobsson I, et al. Cow's milk formula as a cause of infantile colic: a double-blind study. *Pediatrics* 1982;70:7-10.
10. Lothe L, Lindberg T. Cow's milk whey protein elicits symptoms of infantile colic in colicky formula-fed infants: a double-blind crossover study. *Pediatrics* 1989;83:262-6.
11. Forsyth BW. Colic and the effect of change in formulas: a double-blind, multiple-crossover study. *J Pediatr* 1989;115:521-6.
12. Hill DJ, Firer MA, Shelton MJ, et al. Manifestations of milk allergy in infancy: clinical and immunologic findings. *J Pediatr* 1986;109:270-6.
13. Barr RG, Kramer MS, Boisjoly C, et al. Parental diary of infants cry and fuss behaviour. *Arch Dis Child* 1988;63:380-7.
14. Hill DJ, Menahem S, Hudson I, et al. Charting infant distress: an aid to defining colic. *J Pediatr* 1992;121:755-8.
15. Wessel MA, Cobb SC, Jackson EB, et al. Paroxysmal fussing in infancy: sometimes called "colic". *Pediatrics* 1954;14:421-4.
16. Hill DJ, Ball G, Hosking CS. Clinical manifestations of cow's milk allergy in childhood. I. Association with in vitro cellular immune responses. *Clin Allergy* 1988;18:469-79.
17. Hill DJ, Duke AM, Hosking CS, et al. Clinical manifestations of cow's milk allergy in childhood. II. The diagnostic value of skin tests and RAST. *Clin Allergy* 1988;5:481-90.
18. Ford RPK, Barnes GL, Hill DJ. Gastrointestinal hypersensitivity to cow's milk protein: the diagnostic value of gut function tests. *Aust Paediatr J* 1986;22:37-42.
19. Bishop JM, Hill DJ, Hosking CS. Natural history of cow milk allergy: clinical outcome. *J Pediatr* 1990;116:862-7.
20. Hill DJ, Firer MA, Ball G, et al. Recovery from milk allergy in early childhood: antibody studies. *J Pediatr* 1989;114:761-6.
21. Hunziker UA, Barr RG. Increased carrying reduces infant crying: a randomized control trial. *Pediatrics* 1986;77:641-8.
22. Barr RG, McMullan SJ, Speiss H, et al. Carrying as colic "therapy": a randomized control trial. *Pediatrics* 1991;87:623-30.
23. Epi Info Version 5, 1991. Stone Mountain, Georgia: USA Incorporated, 1991.
24. Anderson S, Auquier A, Hauck WW, et al. Statistical methods for comparative studies. Techniques for bias reduction. New York: J. Wiley, 1980.
25. Pocock SJ. Clinical trials, a practical approach. Chichester: Wiley, 1983:123-8.
26. Donner A. Approaches to sample size estimation in the design of clinical trials: a review. *Stat Med* 1984;3:199-214.
27. The GLIM system: release 3.77 manual. Oxford: Numerical Algorithms Group, 1992.
28. Minitab reference manual: release 8.2. State College, Pennsylvania: Minitab Inc, 1991.
29. SPSS-X users guide. 3rd ed. Chicago: SPSS Inc., 1988.
30. Rautava P, Helenius H, Lehtonen L. Psychosocial predisposing factors for infantile colic. *BMJ* 1993;307:600-4.
31. Taubman B. Parental counseling compared with elimination of cow's milk or soy milk protein for the treatment of infant colic syndrome: a randomized trial. *Pediatrics* 1988;81:756-61.
32. Kahn A, Mozin MJ, Rebuffat E, et al. Milk intolerance in children with persistent sleeplessness: a prospective double blind cross-over evaluation. *Pediatrics* 1989;84:595-603.
33. Hill DJ, Ball G, Hosking CS, Wood PR. Gamma-interferon production in cow-milk allergy. *Allergy* 1993;48:75-80.
34. Taubman B. Clinical trial of the treatment of colic by modification of parent-infant interaction. *Pediatrics* 1984;74:998-1003.
35. Wolke D, Gray P, Meyer R. Excessive infant crying: a controlled study of mothers helping mothers. *Pediatrics* 1994;94:322-32.
36. Lachenbruch PA. A note on sample size computation for testing interactions. *Stat Med* 1988;7:467-9.

APPENDIX

Post hoc power analysis

The initial determination of sample size, based on the data available,^{6, 10} underestimated the incidence of spontaneous improvement by up to 30%. A post hoc power analysis³⁶ showed that the numbers required to test the secondary hypothesis was achieved only in the group of breast-fed infants older than 8 weeks of age.