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Review article

Dietary exclusions for improving established atopic eczema in adults and children: systematic review

Atopic eczema is the most common inflammatory skin disease of childhood in developed countries. We performed a systematic review of randomized controlled trials to assess the effects of dietary exclusions for the treatment of established atopic eczema. Nine trials (421 participants) were included, most of which were poorly reported. Six were studies of egg and milk exclusion (n = 288), one was a study of few foods (n = 85) and two were studies of an elemental diet (n = 48). There appears to be no benefit of an egg- and milk-free diet in unselected participants with atopic eczema. There is also no evidence of benefit in the use of an elemental or few-foods diet in unselected cases of atopic eczema. There may be some benefit in using an egg-free diet in infants with suspected egg allergy who have positive specific IgE to eggs – one study found 51% of the children had a significant improvement in body surface area with the exclusion diet as compared with normal diet (95% CI 1.07–2.11) and change in surface area and severity score was significantly improved in the exclusion diet as compared with the normal diet at the end of 6 weeks (MD 5.50, 95% CI 0.19–10.81) and end of treatment (MD 6.10, 95% CI 0.06–12.14). Despite their frequent use, we find little good quality evidence to support the use of exclusion diets in atopic eczema.

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Food hypersensitivity may be the first stage in the development of 'allergic diseases' such as atopic eczema (1). Food allergy may be an important factor in up to 20% of children with atopic eczema under 4 years (2). The incidence of food allergy is highest around the age of 6–9 months. Many clinicians have found that elimination of specific foods found by food challenge to elicit symptoms can lead to significant improvement in eczematous symptoms (3). Challenges in food-allergic patients can lead to eczematous lesions and infiltration of allergic inflammatory cells and animal studies have suggested that eczema may be caused by food allergies (4).

However, many food reactions in people with atopic eczema may not necessarily be mediated through immune reactions (5). As sensitization to food early in life may be a predisposing factor (6) it is important to investigate whether the elimination of dietary triggers could help to alleviate the symptoms of atopic eczema. The role of dietary factors in atopic eczema either as a cause or as a treatment, through the use of exclusion diets, remains unclear (2). Many trial researchers advocate double-blind, placebo-controlled food challenges to establish whether a child has a true food allergy (7).

There is a vast amount of literature claiming that dietary elimination causes improvement of atopic eczema in some cases. However, much of the evidence fails to withstand close scrutiny (5).

The advantage of dietary interventions is that they may address one of the primary causes, as opposed to merely suppressing the symptoms, although there can be serious consequences to any dietary manipulation that leaves the individual deficient in calories, protein or minerals such as calcium (8, 9). Avoidance of multiple foods is potentially hazardous and requires continued paediatric and dietary supervision (8).

Many people, with or without their doctor's or dietician's help, experiment by excluding a particular food suspected of causing a reaction for a variable time. Most investigators would base elimination diets upon proven food allergies, either by challenge or serum food-specific IgE antibodies exceeding specific diagnostic decision points (10).

Because of the uncertainties of the benefits and harms of dietary exclusion in people with atopic eczema, we conducted a systematic review of all relevant randomized controlled trials. A more detailed version of this review has already been published in the Cochrane Library (11).

Methods

Participants and studies

We assessed the effects of general dietary avoidance practices for the treatment of established atopic eczema. We included randomized controlled trials of dietary exclusion for the treatment of established atopic eczema. We excluded double-blind, placebo-controlled food challenges conducted in isolation, as these are not therapeutic trials but diagnostic or provocation tests. Comparisons considered were active exclusion diet *vs* control or a comparison of two active diets. We included participants who had atopic eczema diagnosed by a doctor. In the National Health Service Technology Assessment (HTA) systematic review of treatments for atopic eczema (12), specific terms were used to identify trial participants as listed in Table 1. The list classifies conditions into 'definite', 'possible' and 'not' atopic eczema and we have used this list as a guide. We excluded those studies using terms in the 'not atopic eczema' category such as 'allergic contact eczema'. We found some studies using terms in the 'possible atopic eczema' category, such as 'childhood eczema'. One or more authors scrutinized these and we included them if the description of the participants clearly indicated atopic eczema (i.e. itching and flexural involvement). We included studies with exclusions of any type of food, either singly or in combination with other foods.

Outcomes

Primary outcome measures were: Short-term (within 6 weeks) changes in parent-rated or mother-rated symptoms of atopic eczema such as itching (pruritus) or sleep loss; long-term (over 6 months) such as reduction in number of flares or reduced need for other treatments. Secondary outcome measures were: Global severity as rated by the participants or their physician. Where the outcome was not available, then the following was used: Global changes in composite rating scales using a published named scale; the trial author's modification of existing scales or new scales. Additional secondary outcomes included: Quality of life (13, 14); palatability of the diet and adverse events including long-term consequences on growth. Tertiary outcome measures included changes in individual signs of atopic eczema as assessed by a physician e.g. erythema (redness), purulence (pus formation), excoriation (scratch marks), xerosis (skin dryness), lichenification (thickening of the skin), fissuring (cracks), exudation (weeping serum from the skin surface), pustules (pus spots), papules (spots that protrude from the skin surface), vesicles (clear fluid or 'water blisters' in the skin), crusts (dried serum on skin surface), infiltration/ oedema (swelling of the skin), induration (a thickened feel to the skin).

Searches

We searched the Cochrane Skin Group Specialised Register, Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, LILACS (Latin American and Caribbean Health Science Information database), AMED (Allied and Complementary Medicine) and ISI Web of Science (last search March 2006). The full search strategy has been published elsewhere (11). References from published studies were checked for further trials.

Two of us (FB-H and FD) independently selected the trials for inclusion and extracted the data using a data extraction form for consistency. We resolved any discrepancies by discussion. One of us (FB-H) entered the data. Our quality assessment included an evaluation of: method of generation of the randomization sequence; method of allocation concealment; blinding and number of participants lost to follow up in each arm, and whether participants were analysed in the groups to which they were originally randomized. We also noted the degree of certainty that the participants had atopic eczema; baseline comparability of the participants for age, gender and eczema severity; and assessment of compliance with treatment. A table of quality criteria has been published elsewhere (11).

Statistical methods

For studies with a similar type of intervention, we performed a meta-analysis using Review Manager (15), to calculate a weighted treatment effect across trials, using a random effects model. We have expressed the results as risk ratio (RR) and 95% confidence intervals (CI) for dichotomous outcomes and mean differences (MD and 95% CI) for continuous outcomes. Where it has not been possible to perform a meta-analysis the data has been summarized for each trial.

Heterogeneity was assessed using I^2. Where substantial heterogeneity ($I^2 > 50\%$) existed between studies for the primary outcome, we have explored the reasons for heterogeneity, such as disease severity, whether food allergy was confirmed by a prior provocation/serum test, dosage etc.

Where patient-rated symptoms were reported on categorical Likert scales e.g. no improvement, mild improvement, good improvement, excellent, we dichotomized the data by defining a cut-off at 'good-to-excellent improvement'. Where data was reported on continuous scales e.g. number of days sleep loss, we regarded a 20% reduction/improvement as compared with control as being clinically significant. Not enough studies used SCORAD for us to be able to split eczema severity into mild, moderate and severe where mild is 0–15, moderate is 15–40 and severe is >40.

Where data on existing medication usage was included we have attempted to see whether this has increased differentially in one of the treatment arms as the main dietary intervention has proceeded.

Where paired data was available for cross-over studies, we calculated the conditional odds ratio with 95% CI using the methodology as described by Elbourne 2003 – If paired data was not available then data, where available, was taken from the first phase of the cross-over study and if appropriate then the first phase was treated as a parallel study. Cross-over studies are not ideal for dietary exclusion studies as carry-over effects may invalidate data in the second period. Non randomized controlled studies are listed but not discussed further. Studies relating to adverse effects are described qualitatively.

Results

Description of studies

We identified 12 RCTs of which nine were included. We excluded three studies as they did not fit our inclusion criteria for 'types of intervention' (16–18).

Only two studies were considered sufficiently similar to pool (19, 20).

The studies fell into three main categories; Egg and cow's milk exclusion diets, few-foods diet and elemental diet. The main characteristics of the trials are shown in Table 1. Additional details on methods, interventions and data extraction appear in a more extensive table in the Cochrane review (11) which also lists the three excluded studies and reasons for exclusion.

Risk of bias in the included studies

For seven of the studies the method of randomization was either unclear or not described at all. Two of the studies used a random number table (21, 22). In none of the studies did the trial authors clearly demonstrate adequate concealment of allocation.

Only one study blinded participants, clinicians and outcome assessors (23). Two studies blinded participants and outcome assessors (24, 25). Three studies blinded the outcome assessor only (22, 26, 27). In three studies blinding was unclear (19–21).

In many of the studies, analysis of outcome was carried out only in those participants who completed the study. Only one study analysed by intention-to-treat (20). For one study (19) it was impossible to know if the analysis was intention-to-treat as no results tables were given or numbers mentioned in the text. All but two studies stated numbers and reasons for participants lost to follow up. One study (20) had no loss to follow up, possibly because of the highly selected population.

The certainty of AE was clear for four studies (19, 21–23) that used criteria by Hanifin or Yates. One study stated that they included clinically typical AE (24) and all the other studies did not state how they diagnosed AE.

In one study, the diet group had slightly more extensive and more severe involvement than the controls (27). Two studies clearly stated that there were no differences in baseline comparability (19, 22). For all other studies, it was not clear if there was baseline comparability of the participants.

Compliance was clear in only three studies (22, 23, 25).

Severity of AE was clear in only one study (23).

Egg and cows milk exclusion diets. Six studies (three cross-over studies (21, 24, 25) and three parallel studies) looked at egg and cows milk exclusion diets.

All three cross-over studies were conducted in different populations and used soya milk as a control food which in itself can be allergenic in atopic eczema. All three studies measured severity of AE in different ways. For these reasons the studies were not considered suitable for pooling. Two of the studies (24, 25) gave results for the primary outcome. One study (24) found that pruritus improved during the trial diet as compared with the control diet. A small non significant order effect (i.e. improvements greater at the end of the first *vs* the second period whatever the diet content) with pruritus scores being lower during the first diet period than during the second diet period. Sleeplessness was significantly lower during the trial period as compared with control period ($P < 0.05$), and the order effect was greater than the treatment effect. The same study also reported fewer antihistamines being used in the trial period. The other study (25) reported no significant difference in total itch at the end of trial diet as compared with end of normal diet and found more topical steroids were used on the trial diet. From one of the studies (24), we calculated the difference between the proportions of children whose activity score improved and those whose score did not improve based on paired observations from the same individual. Eczema activity scores improved significantly for children on the exclusion diet as compared with the control diet (Conditional OR 10.52, 95% CI 2.27, 48.80.

No primary outcome data were available for the three parallel studies of egg and cow's milk exclusion. Pooled data from two of the studies (19, 20) found no difference in eczema severity (using the SCORAD index) at 2 to 3 months (pooled analysis, two studies, MD 0.00, 95% CI −4.87 to 4.87) or 6–8 months (pooled analysis, two studies, MD 1.06, 95% CI −1.67 to 3.80; Fig 1). A third study (27) found that at the end of the study, 51% of the children had a significant improvement in body surface area with the exclusion diet as compared with normal diet (RR 1.51, 95% CI 1.07–2.11). Change in surface area and severity score (six clinical features on a scale of 0–3 units at 16 body sites) was significantly improved in the egg exclusion diet group as compared with the normal diet at the end of 6 weeks and end of treatment (MD 5.50, 95% CI 0.19–10.81 and MD 6.10, 95% CI 0.06–12.14; Fig 2) respectively.

Few-foods diet. One few-foods diet study (22) found no significant difference in daytime itch when comparing: few-foods diet with casein as compared with normal diet (MD −0.6, 95% CI, −1.46 to 0.26; Fig 3); few-foods diet with whey as compared with few-foods with casein (MD 0.5, 95% CI, −1.69 to 2.69; Fig 4); few-foods with whey *vs* normal diet (MD −0.10, 95% CI, −2.22 to 2.02; Fig 5). There were no significant differences in sleep disturbances at 6 weeks for: few-foods with whey *vs* normal diet (MD −0.30, 95% CI −2.51 to1.91; Fig 5); few-foods with casein *vs* normal diet (MD −0.10, 95% CI −0.90 to 0.70; Fig 3); few-foods with whey *vs* few-foods with casein (MD −0.20, 95% CI −2.50 to 2.10; Fig 4).

There were no significant differences in body surface area affected at 6 weeks when comparing: few-foods and casein diet *vs* normal diet, (MD −0.10, 95% CI−18.91 to 18.71; Fig 3); few-foods and whey *vs* normal diet (MD −12.90, 95% CI −31.21 to 5.41; Fig 5); few-foods and whey *vs* few-foods and casein (MD −12.80, 95% CI −36.75 to 11.15; Fig 4). There were no significant differences in skin severity score at 6 weeks when comparing: few-foods and whey diet *vs* normal diet (MD−5.9, 95% CI −29.35 to17.55; Fig 5); few-foods and casein diet *vs* normal diet (MD 2.40, 95% CI, −22.64 to 27.44; Fig 3); few-foods and whey diet *vs* few-foods and casein diet (MD −8.3, 95% CI −37.62 to 21.02; Fig 4).

Elemental diets. Two Elemental diet studies, one cross--over study (26) and one parallel study (23). The Munkvad study found no significant difference between the two groups for the combined outcome of pruritus,

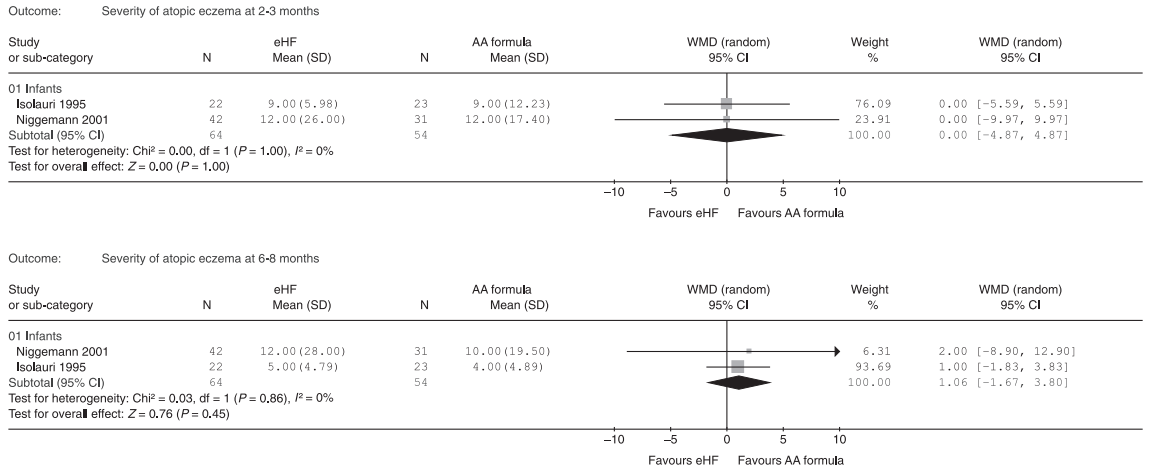

Figure 1. Extensively hydrolysed whey formula (eHF) *vs* Amino Acid (AA) formula.

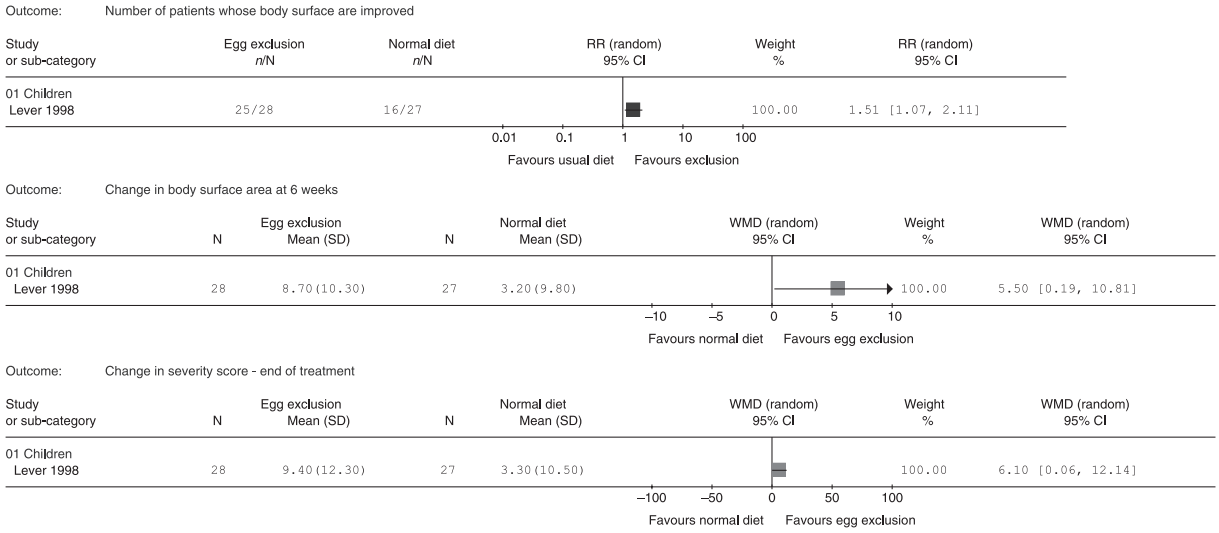

Figure 2. Egg Exclusion *vs* Normal diet.

sleeplessness and antihistamine usage (RR 1.69, 95% CI 0.2 to 13.93). They also found no significant difference at 3 weeks between the two groups for improvement of intensity and extension of the eczema (RR 0.7, 95% CI, 0.25 to 1.97) as measured by a major activity score. A major activity score of > 100 was the criterion for a positive response to treatment. However, there was a non significant trend in favour of the normal diet. The study by Leung found no significant difference in eczema severity score.

Discussion

Main findings

We found some evidence to support the use of an egg-free diet in infants with a suspected egg allergy who have a positive specific IgE to eggs in their blood. This perhaps highlights the importance of allergy testing beforehand. Only two of the other 11 included studies tested for food allergy (19, 20), but those studies dealt with comparisons of two different forms of exclusion diets rather than a comparison of an exclusion diet *vs* normal diet, and have therefore not contributed to the question of whether any form of exclusion diet is helpful in such people. The other included studies of unselected people with atopic eczema did not find any evidence of benefit for exclusion diets. It is useful to know that exclusion diets given to unselected people with atopic eczema are not likely to be helpful, as benefit from dietary exclusions could be because of non allergic mechanisms. Not showing any benefit from such dietary exclusions in unselected people does not mean they are not helpful in people with proven allergy to that particular food, Three of the RCTs used potentially allergenic soya-based milk substitute, which itself can be

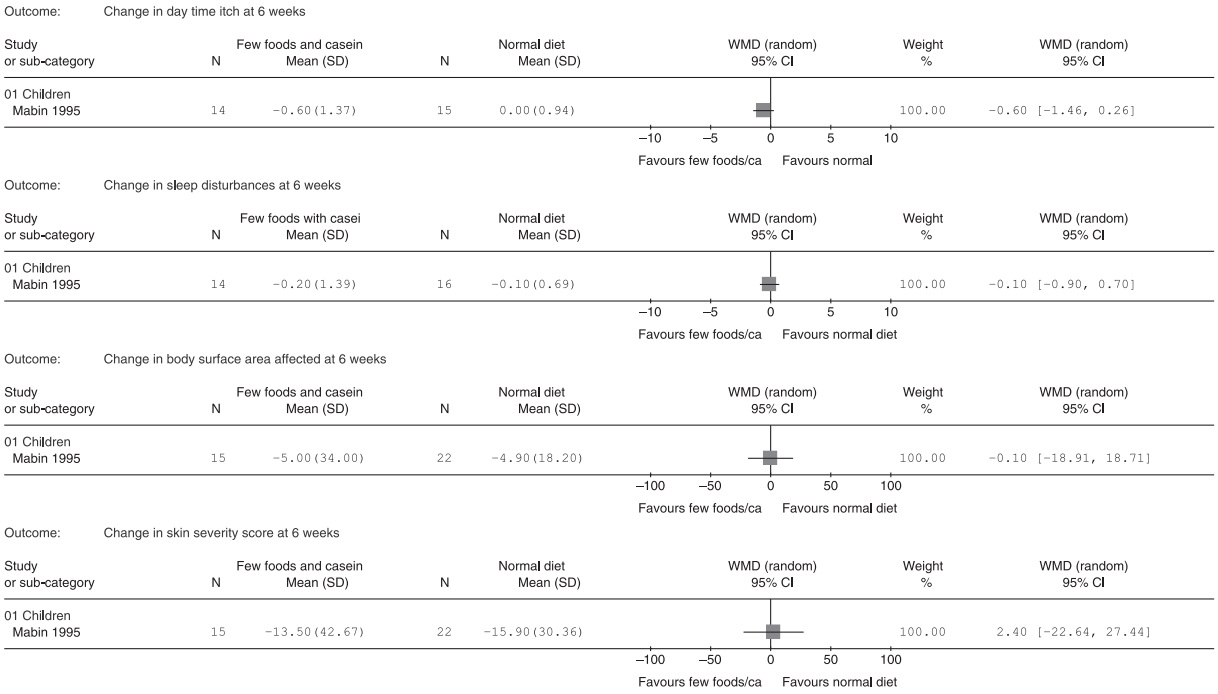

Figure 3. Few Foods diet with casein *vs* Normal diet.

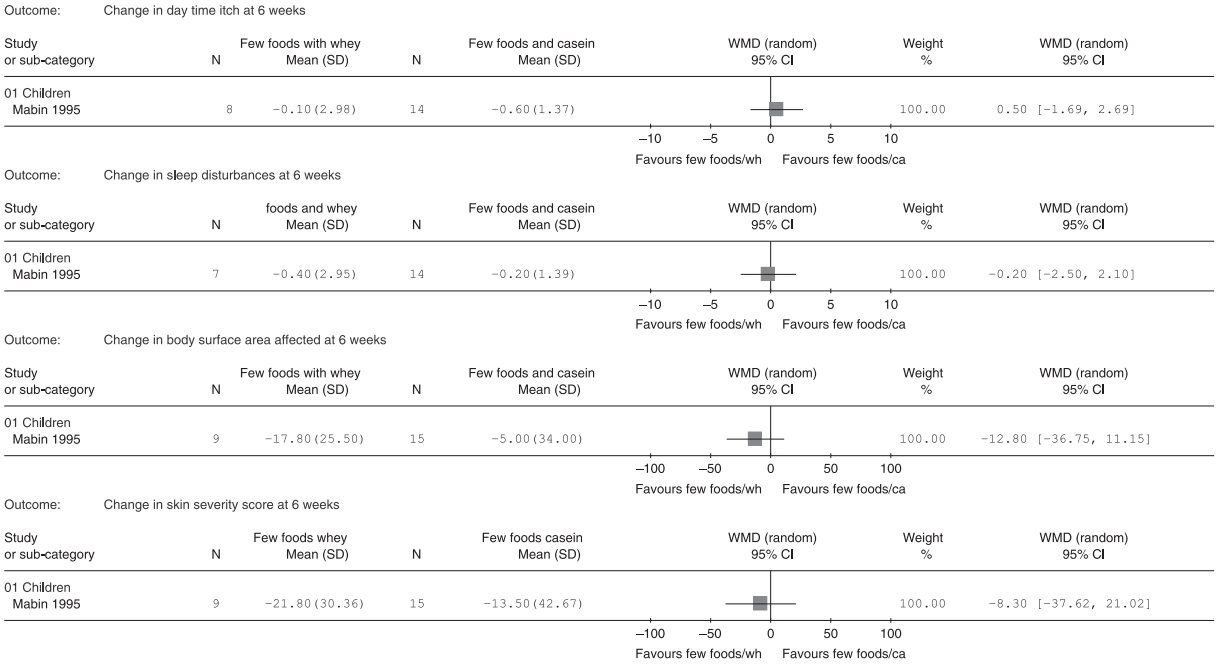

Figure 4. Few Foods diet with whey *vs* Few Foods with casein.

allergenic in atopic eczema. Adverse events for people on exclusion diets included gastrointestinal symptoms followed by exacerbation of eczema or just exacerbation of eczema.

One study of the few-foods diet found no significant change in body surface area, skin severity score, sleep disturbances in children when few-foods diet plus whey as compared with few-foods diet plus casein hydrolysate or usual diet.

Two elemental diet studies were unable to find any significant difference in eczema severity when an elemental diet was compared with a normal hospital diet in

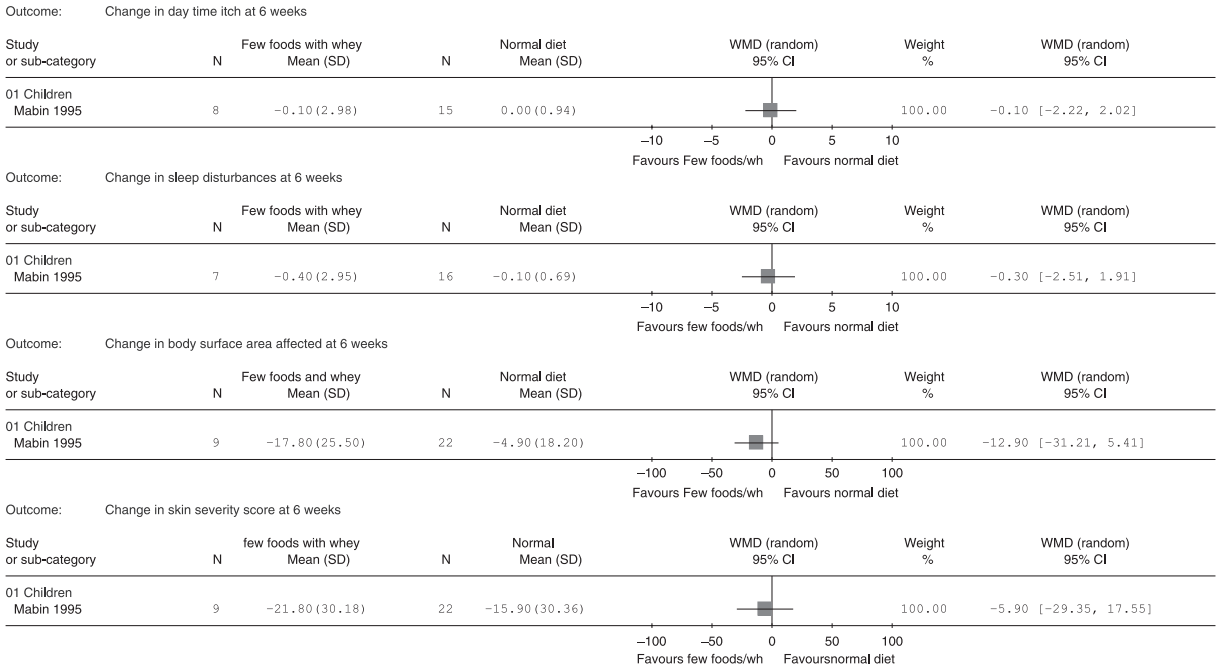

Figure 5. Few Foods with whey *vs* Normal diet.

adults or when an elemental diet was compared with a pre existing formula in children. Elemental diets are difficult as they are unpalatable for many and required hospitalization and dietetic input.

Limitations of this review

We are aware that many of the study participants that were called 'atopic' might not have been and that future studies should use the newly proposed nomenclature.

This systematic review has only addressed dietary exclusion and has not addressed dietary supplements including probiotics, which are the subject of another review. The clinical importance of changes in severity scores obtained in many studies is unknown. Drop-out rates are particularly high for elimination diets and those containing hydrolysate milk substitutes and this will always remain a problem. Overall interpretation of the above studies was difficult because of the poor methodological quality of the studies.

Of the egg- and cow's milk exclusion diets, three studies used soya-based milk substitute, which itself can be allergenic in atopic eczema. Three small cross-over studies studied various populations ranging from infants to adults. Only two studies followed participants for more than 6 months. Long-term outcomes and consequences of an egg and milk-free diet were not discussed by any of the studies. One study in unselected breast feeding mothers and babies found an improvement in their babies' eczema during the exclusion period and when they went back to their normal diet - however possible improvement may well have been spontaneous. One small study in unselected children found a significant improvement in eczema severity during the trials period when an egg and milk exclusion diet was compared with an egg and milk diet, however just under half of the participants were not included in the final analysis. One study in infants (11–17months) with sensitivity to eggs found a significant improvement in body surface area with the exclusion diet when compared with normal diet.

Elimination diets can be difficult to follow. The studies were performed in different populations with only one study giving results on the severity of atopic eczema. The clinical importance of small changes in severity scores obtained in many studies is unknown. Although diets excluding foods such as cows' milk are commonly tried there is little evidence for benefit in their use in unselected people with atopic eczema. That does not mean to say that they could not be beneficial in people with proven cows' milk allergy, but such studies have not been done yet.

Implications for clinical practice and research

Future studies should be large enough to answer the questions posed, and well reported according to CONSORT guidance (28). Common sense suggests that studies of food allergy exclusions should be done on people with a history of suggested food allergy, confirmed by appropriate allergy testing or challenge tests. A distinction should be made between young children, grown-up children and adults, because food allergy in children tends to improve in time. Disease severity should be measured using valid instruments and include quality of life assessments and

patient-centred outcomes that are easy to interpret clinically. Where possible, long-term outcomes (greater than 6 months) should also be recorded in such studies.

Potential conflict of interest

None known.

References

1. Chandra RK. Food hypersensitivity and allergic diseases. Eur J Clin Invest 2002;**56**(Suppl. 13):S54–S56.
2. Oranje A, De Waard-van der Spek F. Atopic dermatitis and diet. J Eur Acad Dermatol Venereol 2000;**14**:437–438.
3. Sampson HA. The evaluation and management of food allergy in atopic dermatitis. Clin Dermatol 2003;**21**: 183–192.
4. Li XM, Kleiner GA, Huang CK, Lee SY, Schofield BH, Soter NA. Murine model of atopic dermatitis associated with food hypersensitivity. J Allergy Clin Immunol 2001;**107**:693–702.
5. David TJ, Patel L, Ewing CI, Stanton RHJ. Dietary factors in established atopic dermatitis. in: Williams H, editor. The epidemiology, causes and prevention of atopic dermatitis. Cambridge University Press, 2000: 193–201.
6. Baena-Cagnani C, Teijeiro A. Role of food allergy in asthma in childhood. Curr Opin Allergy Clin Immunol 2001;**1**:145–149.
7. Sampson H. The immunopathogenic role of food hypersensitivity in atopic dermatitis. Acta Derm Venereol 1992;**176**:34–37.
8. David TJ, Waddington E, Stanton R. Nutritional hazards of elimination diets in children with atopic dermatitis. Arch Dis Child 1984;**59**:323–325.
9. Devlin J, Stanton RHJ, David TJ. Calcium intake and vows' milk free diets. Arch Dis Child 1989;**64**: 1183–1184.
10. Sampson HA. Utility of food-specific IgE concentrations in predicting symptomatic food allergy. J Allergy Clin Immunol 2001;**107**:891–896.
11. Bath-Hextall F, Delamere FM, Williams HC. Dietary exclusions for established atopic eczema (Review). Cochrane Database Syst Rev, 2008: Art. No.: CD005203. DOI: 1002/ 14651858.CD005203. pub2.
12. Hoare C, Li Wan Po A, Williams HC. Systematic review of treatments for atopic eczema. Health Technol Assess (Winchester, England) 2000;**4**:1–191.
13. Chren MM, Lasek RT, F;pcle SA, Zyzanski SJ. Improved discriminative and evaluative capability of a refined version of SKINDEX, a quality-of-life instrument for patients woth skin diseases. Arch Dermatol 1997;**133**: 1433–1440.
14. Finlay AY. Measurement of disease activity and outcome in atopic dermatitis. Br J Dermatol 1996;**135**: 509–515.
15. Review Manager (RevMan) Copenhagen:The Nordic Cochrane Centre [program]. 4.2 for Windows version, 2003.
16. Majamaa H, Isolauri E. Probiotics: A novel approach in the management of food allergy. J Allergy Clin Immunol 1997;**99**:179–185.
17. Isolauri E, Arvola T, Sutas Y, Moilanen E, Salminen S. Probiotics in the management of atopic eczema. Clin Exp Allergy 2000;**30**:1604–1610.
18. Kirjavainen PV, Salminen SJ, Isolauri E. Probiotic bacteria in the management of atopic disease:underscoring the importance of viability. J Pediatr Gastroenterol Nutr 2003;**36**:223–227.
19. Niggemann B, Binder C, Dupont C, Hadji S, Arvola T, Isolauri E. Prospective, controlled, multi-center study on the effect of an amino-acid-based formula in infants with cow's milk allergy/ intolerance and atopic dermatitis. Pediatr Allergy Immunol 2001;**12**: 78–82.
20. Isolauri E, Sutas Y, Makinen-Kiljunen S, Oja S, Isosomppi R, Turjanmaa K. Efficacy and safety of hydrolyzed cow milk and amino acid-derived formulas in infants with cow milk allergy. J Pediatr 1995;**127**:550–557.
21. Cant J, Bailes J, Marsden R, Hewitt D. Effect of maternal dietary exclusion on breast fed infants with eczema: two controlled studies. BMJ 1986;**26**(July): 231–233.
22. Mabin D, Sykes A, David TJ. Controlled trial of a few foods diet in severe atopic dermatitis. Arch Dis Child 1995;**73**:202–207.
23. Munkvad M, Danielsen L, Hoj L, Povlsen C, Secher L, Svejgaard E et al. Antigen-free diet in adult patients with atopic dermatitis. Acta derm venereol (Stockh) 1984;**64**:524–528.
24. Atherton D, Soothill J, Sewell M, Wells R. A double-blind controlled crossover trial of an antigen-avoidance diet in atopic eczema. Lancet 1978;**25**:401–403.
25. Neild V, Marsden R, Bailes J, Bland J. Egg and milk exclusion diets in atopic eczema. Br J Dermatol 1986;**114**: 117–123.
26. Leung TF, Ma KC, Cheung LTF, Lam CWK, Wong E, Wang H. A randomised, single-blind and crossover study of an amino acid-based milk formula in treating young children with atopic dermatitis. Pediatr Allergy Immunol 2004;**1004**:558–561.
27. Lever R, MacDonald C, Waugh P, Aitchison T. Randomised controlled trial of advice on an egg exclusion diet in young children with atopic eczema and sensitivity to eggs. Pediatr Allergy Immunol 1998;**9**:13–19.
28. Moher D, Schulz KF, Altman DG, Lepage L. The CONSORT statement: revised recommendations for improving the quality of reprts of parallel group randomised trials. Lancet 2001; **357**:1191–1194.

