

Maternal dietary antigen avoidance during pregnancy or lactation, or both, for preventing or treating atopic disease in the child (Review)

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[Intervention Review]

Maternal dietary antigen avoidance during pregnancy or lactation, or both, for preventing or treating atopic disease in the child

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ABSTRACT

Background

Some breastfed infants with atopic eczema benefit from elimination of cow milk, egg, or other antigens from their mother's diet. Maternal dietary antigens are also known to cross the placenta.

Objectives

To assess the effects of prescribing an antigen avoidance diet during pregnancy or lactation, or both, on maternal and infant nutrition and on the prevention or treatment of atopic disease in the child.

Search methods

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (6 July 2012).

Selection criteria

All randomized or quasi-randomized comparisons of maternal dietary antigen avoidance prescribed to pregnant or lactating women. We excluded trials of multimodal interventions that included manipulation of the infant's diet other than breast milk or of non-dietary aspects of the infant's environment.

Data collection and analysis

We extracted data from published reports, supplemented by additional information received from the trialists we contacted.

Main results

The evidence from five trials, involving 952 participants, does not suggest a protective effect of maternal dietary antigen avoidance during pregnancy on the incidence of atopic eczema during the first 18 months of life. Data on allergic rhinitis or conjunctivitis, or both, and urticaria are limited to a single trial each and are insufficient to draw meaningful inferences. Longer-term atopic outcomes

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have not been reported. The restricted diet during pregnancy was associated with a slightly but statistically significantly lower mean gestational weight gain, a non-significantly higher risk of preterm birth, and a non-significant reduction in mean birthweight.

The evidence from two trials, involving 523 participants, did not observe a significant protective effect of maternal antigen avoidance during lactation on the incidence of atopic eczema during the first 18 months or on positive skin-prick tests to cow milk, egg, or peanut antigen at one, two, or seven years.

One crossover trial involving 17 lactating mothers of infants with established atopic eczema found that maternal dietary antigen avoidance was associated with a non-significant reduction in eczema severity.

Authors' conclusions

Prescription of an antigen avoidance diet to a high-risk woman during pregnancy is unlikely to reduce substantially her child's risk of atopic diseases, and such a diet may adversely affect maternal or fetal nutrition, or both. Prescription of an antigen avoidance diet to a high-risk woman during lactation may reduce her child's risk of developing atopic eczema, but better trials are needed.

Dietary antigen avoidance by lactating mothers of infants with atopic eczema may reduce the severity of the eczema, but larger trials are needed.

PLAIN LANGUAGE SUMMARY

Maternal dietary antigen avoidance during pregnancy or lactation, or both, for preventing or treating atopic disease in the child

Evidence is inadequate to advise women to avoid specific foods during pregnancy or breastfeeding to protect their children from allergic diseases like eczema and asthma.

We included five trials, involving 952 participants. Trials of mothers' avoidance of milk, eggs, and other potentially 'antigenic' foods during pregnancy or breastfeeding, or both, provide inadequate evidence about whether such avoidance helps prevent atopic eczema or asthma in the child. Women who avoided eating these foods gained significantly less weight during pregnancy in the one trial reporting on this outcome, raising the possibility of adverse nutritional effects on the mother or fetus. Finally, one small trial reported an inconclusive response of breastfed infants with atopic eczema when their mothers avoided consumption of cow milk and egg.

BACKGROUND

Atopic (allergic) diseases such as eczema, asthma, allergic rhinitis or conjunctivitis, or both, (hay fever), and urticaria (hives) are known to have a strong genetic component, but the increased incidence and severity of asthma and perhaps of other atopic diseases over the last few decades (Upton 2000; Williams 1992; Woolcock 1997) underlines the etiologic importance of environmental factors. Maternal dietary antigens are known to cross the placenta (Loibichler 2002) and pass into breast milk (Cant 1985; Jakobsson 1985; Shannon 1921; Stuart 1984; Troncone 1987; Vadas 2001). A recent study, however, found that inhalant and food antigen-specific IgE in cord blood reflected maternal IgE but was no longer present in the infant's blood at six months of age, suggesting that the infant is not sensitized to those antigens through in utero exposure (Bonnellykke 2008). Some cases of atopic eczema in breastfed infants have been reported to improve following elimination of of-

fending antigens ingested by the mother during lactation (Gerrard 1979; O'Keefe 1920; Talbot 1918). The diagnosis of allergic diseases is somewhat subjective, and the clinical course of these diseases is highly variable. (Although positive skin prick tests to specific antigens indicate that the subject is allergic to those antigens and suggest a general atopic diathesis, persons with allergic diseases do not always react with positive skin tests, and many persons with positive skin tests do not exhibit signs or symptoms of these diseases.) Methodologically rigorous trials are therefore necessary to establish the efficacy of maternal dietary antigen avoidance during pregnancy or lactation, or both (Zeiger 2003).

OBJECTIVES

To assess the effects of prescribing an antigen avoidance diet during pregnancy or lactation on the nutritional status of the mother and

newborn and on the development of atopic disease in the child; positive skin prick tests to dietary antigens; and cord blood levels of IgE (a predictor of subsequent atopic disease). The main focus is on women at high risk for giving birth to an atopic child, based on a history of atopic disease in the mother, father, or a previous child.

The review also assesses the effects of prescribing an antigen avoidance diet to lactating mothers of infants with established atopic eczema on the severity of the eczema.

METHODS

Criteria for considering studies for this review

Types of studies

All acceptably controlled (randomized or quasi-randomized) comparisons of maternal dietary antigen avoidance prescribed to pregnant (at any time during pregnancy) or lactating women at high risk, regardless of degree (number of foods eliminated from the diet) or duration. We have included trials comparing groups of women randomized to diets containing different levels of potential antigens, even if the experimental treatment involved only a reduction in antigen exposure, rather than total avoidance. We have also included data on breastfed infants in trials in which the maternal antigen avoidance began during pregnancy and continued into the lactation period. We have excluded, however, trials of multimodal interventions that include, in addition to maternal dietary antigen avoidance, manipulation of the infant's diet other than breast milk or of other non-dietary aspects of the infant's environment (i.e., exposure to inhaled allergens). Finally, we have also included all acceptably controlled (randomized or quasi-randomized) comparisons of maternal antigen avoidance prescribed to lactating mothers of infants with atopic eczema, regardless of degree or duration.

Types of participants

Pregnant or lactating women at high risk for giving birth to an atopic child, based on a history of atopic disease (eczema, asthma, or hay fever) in the mother, father, or a previous child. Lactating mothers of infants with established atopic eczema.

Types of interventions

Prescription of diet with exclusion (or reduced quantity) of potentially antigenic foods such as cow milk, egg, peanuts, fish, and chocolate.

Types of outcome measures

Primary outcomes

Occurrence and severity of atopic disease in the child.

Secondary outcomes

Nutritional status of mother (gestational weight gain) and fetus (birthweight); other pregnancy outcomes (e.g., preterm birth); positive skin prick tests to ingested antigen (especially egg and milk); and cord blood IgE levels.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register by contacting the Trials Search Co-ordinator (6 July 2012).

The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:

1. monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE;
3. weekly searches of EMBASE;
4. handsearches of 30 journals and the proceedings of major conferences;
5. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Details of the search strategies for CENTRAL, MEDLINE and EMBASE, the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the 'Specialized Register' section within the editorial information about the [Cochrane Pregnancy and Childbirth Group](#).

Trials identified through the searching activities described above are each assigned to a review topic (or topics). The Trials Search Co-ordinator searches the register for each review using the topic list rather than keywords.

We did not apply any language restrictions.

Data collection and analysis

For the methods used when assessing the trials identified in the previous version of this review, see [Appendix 1](#)

For this update we used the following methods when assessing the trials identified by the updated search:

Selection of studies

Two review authors independently assessed for inclusion all the potential studies we identified as a result of the search strategy. We resolved any disagreement through discussion or, if required, we would have consulted a third person.

Data extraction and management

We designed a form to extract data. For eligible studies, two review authors extracted the data using the agreed form. We resolved discrepancies through discussion or, if required, we would have consulted a third person. We entered data into Review Manager software (RevMan 2011) and checked for accuracy.

When information regarding any of the above was unclear, we attempted to contact authors of the original reports to provide further details.

Assessment of risk of bias in included studies

Two review authors independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved any disagreement by discussion or we would have involved a third assessor.

(1) Random sequence generation (checking for possible selection bias)

We described for each included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.

We assessed the method as:

- low risk of bias (any truly random process, e.g. random number table; computer random number generator);
- high risk of bias (any non-random process, e.g. odd or even date of birth; hospital or clinic record number);
- unclear risk of bias.

(2) Allocation concealment (checking for possible selection bias)

We described for each included study the method used to conceal allocation to interventions prior to assignment and assessed whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.

We assessed the methods as:

- low risk of bias (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- high risk of bias (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- unclear risk of bias.

(3.1) Blinding of participants and personnel (checking for possible performance bias)

We described for each included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We considered that studies are at low risk of bias if they were blinded, or if we judged that the lack of blinding would be unlikely to affect results. We assessed blinding separately for different outcomes or classes of outcomes. We assessed the methods as:

- low, high or unclear risk of bias for participants;
- low, high or unclear risk of bias for personnel.

(3.2) Blinding of outcome assessment (checking for possible detection bias)

We described for each included study the methods used, if any, to blind outcome assessors from knowledge of which intervention a participant received. We assessed blinding separately for different outcomes or classes of outcomes.

We assessed methods used to blind outcome assessment as:

- low, high or unclear risk of bias.

(4) Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data)

We described for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We stated whether attrition and exclusions were reported and the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information is reported, or can be supplied by the trial authors, we would re-include missing data in the analyses which we undertook.

We assessed methods as:

- low risk of bias (e.g. no missing outcome data; missing outcome data balanced across groups);
- high risk of bias (e.g. numbers or reasons for missing data imbalanced across groups; 'as treated' analysis done with substantial departure of intervention received from that assigned at randomization);
- unclear risk of bias.

(5) Selective reporting (checking for reporting bias)

We described for each included study how we investigated the possibility of selective outcome reporting bias and what we found. We assessed the methods as:

- low risk of bias (where it is clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);

- high risk of bias (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);

- unclear risk of bias.

(6) Other bias (checking for bias due to problems not covered by 1 to 5 above)

We described for each included study any important concerns we have about other possible sources of bias.

We assessed whether each study was free of other problems that could put it at risk of bias:

- low risk of other bias;
- high risk of other bias;
- unclear whether there is risk of other bias.

(7) Overall risk of bias

We made explicit judgements about whether studies are at high risk of bias, according to the criteria given in the Handbook (Higgins 2011). With reference to (1) to (6) above, we assessed the likely magnitude and direction of the bias and whether we consider it was likely to impact on the findings.

Measures of treatment effect

Dichotomous data

For dichotomous data, we presented results as summary risk ratio with 95% confidence intervals.

Continuous data

For continuous data, we used the mean difference if outcomes are measured in the same way between trials. We used the standardised mean difference to combine trials that measure the same outcome, but use different methods.

Dealing with missing data

In future updates, for included studies, we will note levels of attrition. We will explore the impact of including studies with high levels of missing data in the overall assessment of treatment effect by using sensitivity analysis.

For all outcomes, we will carry out analyses, as far as possible, on an intention-to-treat basis, i.e. we will attempt to include all participants randomised to each group in the analyses, and all participants will be analysed in the group to which they were allocated, regardless of whether or not they received the allocated

intervention. The denominator for each outcome in each trial will be the number randomised minus any participants whose outcomes are known to be missing.

Assessment of heterogeneity

We assessed statistical heterogeneity in each meta-analysis using the T^2 , I^2 and Chi^2 statistics. We would have regarded heterogeneity as substantial if I^2 had been greater than 30% and either T^2 was greater than zero, or there was a low P-value (< 0.10) in the Chi^2 test for heterogeneity.

Assessment of reporting biases

If there had been 10 or more studies in the meta-analysis, we would have investigated reporting biases (such as publication bias) using funnel plots. We would have assessed funnel plot asymmetry visually, and used formal tests for funnel plot asymmetry. For continuous outcomes we would have used the test proposed by Egger 1997, and for dichotomous outcomes we would have used the test proposed by Harbord 2006. If asymmetry had been detected in any of these tests or was suggested by a visual assessment, we would have performed exploratory analyses to investigate it.

Data synthesis

We carried out statistical analysis using the Review Manager software (RevMan 2011). We used fixed-effect meta-analysis for combining data where it was reasonable to assume that studies were estimating the same underlying treatment effect: i.e. where trials are examining the same intervention, and the trials' populations and methods are judged sufficiently similar. If there was clinical heterogeneity sufficient to expect that the underlying treatment effects differ between trials, or if substantial statistical heterogeneity was detected, we would have used random-effects meta-analysis to produce an overall summary if an average treatment effect across trials was considered clinically meaningful. The random-effects summary would be treated as the average range of possible treatment effects and we would have discussed the clinical implications of treatment effects differing between trials. If the average treatment effect was not clinically meaningful we would not combine trials.

If we used random-effects analyses, the results were presented as the average treatment effect with 95% confidence intervals, and the estimates of T^2 and I^2 .

Subgroup analysis and investigation of heterogeneity

If we identify substantial heterogeneity in the future, we will investigate it using subgroup analyses and sensitivity analyses. We will consider whether an overall summary is meaningful, and if it is, use random-effects analysis to produce it.

Sensitivity analysis

None undertaken.

RESULTS

Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#).

We identified 12 trials.

Included studies

We included five trials ([Appelt 2004](#); [Cant 1986](#); [Falth-Magnusson 1987](#); [Lilja 1988](#); [Lovegrove 1994](#)), involving 925 participants. For details, see [Characteristics of included studies](#).

Excluded studies

We excluded seven trials ([Arshad 1992](#); [Arshad 2007](#); [Chandra 1986](#); [Chandra 1989](#); [Hattevig 1989](#); [Vance 2004](#); [Zeiger 1989](#)). For details, see [Characteristics of excluded studies](#).

We included two of the excluded studies in the original version of this review ([Chandra 1986](#); [Chandra 1989](#)) but subsequently excluded them because investigations by Chandra's university (Memorial University of Newfoundland) and by the Canadian Broadcasting Corporation strongly suggest that the published data may have been fabricated. The exclusion of these trials does not change the conclusions of the review.

Risk of bias in included studies

The two included trials on antigen avoidance diet during pregnancy are of uneven methodological quality. Only [Falth-Magnusson 1987](#) provided details of the randomization procedure, and neither based its primary analysis on 'intention to treat', i.e., mothers who failed to comply with the antigen avoidance diet were not analyzed as part of their allocated group. In both trials, examinations of children at age 18 months were performed by physicians blind to treatment allocation. We excluded the five-year follow up of the trial by [Falth-Magnusson 1992](#) from analysis because the results are based on the diets actually followed, rather than those allocated by randomization.

Of the two trials of dietary antigen avoidance during lactation, [Lovegrove 1994](#) has methodologic shortcomings: details of the randomization procedure were not provided, and analysis was not based on 'intention to treat' (i.e., mothers who failed to comply with the antigen avoidance diet were not analyzed as part of

their allocated group). Data were provided, however, on compliance with the experimental or control diet, and the physicians who examined study children for evidence for atopic disease were masked, although mothers may have unblinded them. Risk of bias in [Appelt 2004](#) is difficult to judge, because the information available is based solely on a published abstract that provides no details on the method of randomization or on losses to follow-up between randomization and one-year follow-up.

Although two separate trials on antigen avoidance diet for lactating mothers of infants with established atopic eczema are included in [Cant 1986](#), only the first was sufficiently well controlled to warrant inclusion in this review; it used a double-blind, randomized crossover design and is of acceptable quality. (The second trial was an unblinded, non-randomized crossover trial.) For the first (included) trial, the results were analyzed appropriately in the original publication using a paired t-test, but the data presented in the tables in this review are group means at the end of the exclusion (intervention) diet and common standard deviations (i.e., for all study subjects) at the end of the trial after four weeks back on the pre-trial diet.

Effects of interventions

Two trials, involving 334 pregnant women, were included in the review of dietary antigen avoidance during pregnancy ([Falth-Magnusson 1987](#); [Lilja 1988](#)). The combined evidence from the trials does not suggest a strong protective effect of maternal antigen avoidance on the incidence of atopic eczema (risk ratio (RR) 1.01, 95% confidence interval (CI) 0.57 to 1.79) or asthma (RR 2.22, 95% CI 0.39 to 12.67) during the first 18 months of life. Data on allergic rhinitis or conjunctivitis, or both, and urticaria are limited to a single trial each and are insufficient to draw meaningful inferences. Both trials suggest a lower incidence of positive skin prick tests to egg antigen at six months of age, but the effect was no longer evident at 18 months, nor was any benefit apparent at either age for skin prick tests to milk antigen. In the [Lilja 1988](#) trial, cord blood IgE levels were, if anything, higher in the experimental (antigen avoidance) group. Longer-term atopic outcomes have not been reported. Based on the single trial ([Falth-Magnusson 1987](#)) providing pertinent data, the restricted diet during pregnancy was associated with a small but statistically significant lower mean gestational weight gain (mean difference (MD) -3.00, 95% CI -5.21 to -0.79) percentage of pre-pregnancy weight, i.e., 1.8 kg for a 60-kg woman). The pooled results of two trials ([Falth-Magnusson 1987](#); [Lovegrove 1994](#), the latter including an intervention that continued into lactation) suggest that maternal antigen avoidance may be associated with a higher (but statistically highly unstable) risk of preterm birth (RR 10.06, 95% CI 0.53 to 192.26) and a possible adverse effect on mean birthweight (MD -83.45, 95% CI -221.87 to 54.97).

One trial of antigen avoidance during lactation reporting on only 26 lactating women ([Lovegrove 1994](#)) found no significant pro-

protective effect of maternal antigen avoidance on the incidence of atopic eczema during the child's first 18 months of life (RR 0.73, 95% CI 0.32 to 1.64). The two excluded Chandra trials (Chandra 1986; Chandra 1989) both contributed data to this comparison in the original versions of this review. A larger included trial (Appelt 2004) did not report on atopic eczema or other allergic disease outcomes, but found no evidence of sensitization to milk, egg, or peanut antigen on skin-prick testing at one, two, or seven years of age.

One small crossover trial (Cant 1986) involving 17 lactating mothers found that dietary antigen avoidance by mothers of infants with established atopic eczema was associated with a non-significant reduction in eczema severity.

DISCUSSION

Prescription of an antigen avoidance diet to a high-risk woman during pregnancy or lactation is unlikely to reduce substantially her risk of giving birth to an atopic child. More data are necessary on potential adverse effects of maternal antigen avoidance during pregnancy on gestational weight gain, fetal growth, and preterm birth.

The unimpressive results of the single trial assessing restricted diet for lactating mothers of infants with eczema should be interpreted with caution because of its small size ($n = 17$) and because the trial compared exposure to cow milk and egg with exposure to soya milk (soya can itself be allergenic). Future trials should be larger and should ensure adequate antigen restriction of the maternal diet.

AUTHORS' CONCLUSIONS

Implications for practice

Prescription of an antigen avoidance diet to a high-risk woman during pregnancy or lactation is unlikely to reduce substantially her risk of giving birth to an atopic child and may have an adverse

effect on maternal or fetal nutritional status, or both. The original version of this review suggested a possible benefit of antigen avoidance during lactation, but after exclusion of the two trials with suspected data fabrication, the evidence no longer suggests a beneficial effect.

As stated by the authors of the single trial of antigen avoidance in mothers of infants with atopic eczema, "most breastfed babies with eczema do not respond to maternal dietary manipulation." Even if this is so, maternal reports of changes in the severity of their breastfed infants' eczema following ingestion of certain foods should not be summarily dismissed. Rather, such reports should be pursued by performing multiple (preferably double-blinded) challenges and dechallenges with the suspected foods.

Implications for research

Future trials on the effect of maternal dietary antigen avoidance during pregnancy will require much larger sample sizes to detect more modest reductions in risk of atopic disease in infants and children, and longer follow-up will be necessary to detect potential benefits on other atopic outcomes (i.e., allergic rhinitis and conjunctivitis and asthma). More data are required on potential adverse effects of maternal antigen avoidance on gestational weight gain, fetal growth, and preterm birth.

As to the effects of maternal dietary antigen avoidance during lactation, better and larger trials are required, specifically with respect to allergic disease outcomes.

Finally, since adherence to an antigen avoidance diet during pregnancy and/or lactation requires considerable effort, more information is necessary on women's experience and compliance with such diets.

Future trials on the effects of antigen avoidance diet for lactating mothers of infants with established eczema should be larger and should ensure adequate antigen restriction of the maternal diet.

ACKNOWLEDGEMENTS

None.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Appelt 2004

Methods	Randomization method not described.	
Participants	497 Canadian mothers of infants from high-risk families, defined as having at least 1 first-degree relative with asthma or 2 with a history of other IgE-mediated allergy	
Interventions	Experimental: complete avoidance of peanut, nuts, and fish and decreased intake of milk and eggs during the third trimester of pregnancy and while breastfeeding for up to 1 year. A partially hydrolyzed formula supplement was provided for the first year, if required Control: usual care and diet.	
Outcomes	Skin-prick testing for hypersensitivity to cow milk, egg, and peanut antigen at 1, 2, and 7 years	
Notes	Based on published abstract only.	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Published as abstract only; no details provided on randomization

Cant 1986

Methods	Randomized crossover trial based on random numbers table, but details of allocation procedure not reported	
Participants	19 US mothers of infants 6 weeks to 6 months of age with atopic eczema	
Interventions	Experimental: maternal exclusion of cow milk, egg, chocolate, wheat, nuts, fish, beef, chicken, citrus fruits, colorings, and preservatives, with use of soya-based milk substitute for 4 weeks. Control: same dietary exclusions for same duration (4 weeks), but substitute contained cow milk and egg. Each of the 2 interventions allocated to all subjects in randomized order	
Outcomes	2, continuous-scale eczema severity scores evaluated after 4 weeks on each diet: area (number of involved body areas from 0 to 20) and "activity" (severity within each area on 0-3 scale X number of involved areas)	
Notes	1) 2 poor compliers excluded. 2) No data presented on compliance in the 17 women not excluded. 3) Results in original publication analyzed appropriately for crossover trial; data tables in this review contain group means after exclusion diet (intervention vs control) and common	

Cant 1986 (Continued)

	SD for each outcome at the end of the trial. 4) A second, non-randomized crossover trial reported in the same publication has been excluded from this review, because the sequential treatments were used in the same order in all subjects (i.e., not randomized)	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Unclear.

Falth-Magnusson 1987

Methods	Randomization based on random numbers assigned in advance, allocation contained in sealed envelope opened only after consent was obtained	
Participants	212 pregnant Swedish women with positive family history of allergy (herself, husband, or previous children)	
Interventions	Experimental: cow milk and egg avoidance diet from 28 weeks of gestation. Control: normal diet.	
Outcomes	Gestational weight gain, cord blood IgE, atopic eczema, asthma, birthweight, and preterm birth	
Notes	1) Birthweight, 5-year atopic outcomes analyzed by compliance with diet, not by randomized allocation group. 2) SDs for cord blood and maternal IgEs do not add up.	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Adequate

Lilja 1988

Methods	Cluster randomization used in Stockholm/Uppsala, but randomization method not described	
Participants	171 pregnant women in Stockholm/Uppsala with a history of respiratory allergy to pollen and/or dander. 84 pregnant women from Linköping are also mentioned in the 1988 report, but these appear to be a subset of the women reported in Falth-Magnusson 1987 .	
Interventions	Experimental: low-milk and low-egg diet during third trimester. Control: high-milk and high-egg diet during third trimester.	

Lilja 1988 (Continued)

Outcomes	Cord blood IgE, total atopy, asthma, atopic eczema, allergic rhinitis, and urticaria	
Notes	1) Analysis based on individual subjects despite cluster randomization. 2) Small number of non-compliers not analyzed. 3) Large differences at baseline in type of allergy in both trials raises question about randomization. 4) Cord blood IgE levels not tabulated; graph only. 5) Cord blood IgE sample sizes do not add up.	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	High risk	Inadequate.

Lovegrove 1994

Methods	Randomization method not described.	
Participants	Pregnant English women with atopic histories in themselves or in partners, recruited at 30 weeks' gestation	
Interventions	Experimental: milk-free diet from 36 weeks' gestation and during lactation. Control: unrestricted diet.	
Outcomes	Atopic eczema at 6, 12, and 18 months, preterm birth, and birthweight. Atopic outcomes restricted to comparison of antigen avoidance during lactation, while birth outcomes (preterm birth and birthweight) restricted to comparison of antigen avoidance during pregnancy	
Notes	1) Number of women randomized not reported, but 44 original participants included non-atopic women. 2) 6 of 44 total participants (including non-atopic, non-randomized) not included in analysis. 3) Non-blind mothers may have unblinded examining physicians. 4) Funded by manufacturer of hypoallergenic formula.	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	High risk	Inadequate.

SD: standard deviation
vs: versus

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Arshad 1992	Experimental intervention included dietary antigen avoidance in infant's diet, as well as the mother's, and also included application of acaricidal powder to reduce exposure to inhaled dust mite antigen
Arshad 2007	Maternal antigen avoidance during lactation included, in the experimental group, a subgroup of breastfed that was combined with (and inseparable from) a subgroup of non-breastfed infants fed hydrolyzed formula, and both subgroups also received interventions to reduce exposure to house dust mite: acaricide treatment of upholstery and carpets and plastic mattress covers
Chandra 1986	Included in previous versions of this review. Now excluded because investigations by Chandra's university (Memorial University of Newfoundland) and by the Canadian Broadcasting Corporation strongly suggest that the published data may have been fabricated
Chandra 1989	Included in previous versions of this review. Now excluded because investigations by Chandra's university (Memorial University of Newfoundland) and by the Canadian Broadcasting Corporation strongly suggest that the published data may have been fabricated
Hattevig 1989	Experimental and control interventions allocated by site (2 different hospital clinics), not randomized or quasi-randomized
Vance 2004	Offspring atopic outcomes reported only in those with cord serum IgG levels obtained (136 of the 229 randomized), and numbers in each treatment arm not provided
Zeiger 1989	Experimental intervention included dietary antigen avoidance in infant's diet, as well as the mother's. In addition, the trial suffered from large and grossly unequal losses to follow up due to non-compliance with dietary restriction

DATA AND ANALYSES

Comparison 1. Maternal antigen avoidance in pregnancy in women at high risk for atopic offspring

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Atopic eczema in first 12-18 months	2	334	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.57, 1.79]
2 Asthma in first 18 months	2	334	Risk Ratio (M-H, Random, 95% CI)	2.22 [0.39, 12.67]
3 Allergic rhinitis/conjunctivitis in first 18 months	1	163	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Allergic urticaria in first 18 months	1	163	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.21, 4.87]
5 Any atopic condition in first 18 months	1	163	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.42, 1.38]
6 Positive skin prick test to egg at 6 months	2	340	Risk Ratio (M-H, Random, 95% CI)	0.58 [0.32, 1.05]
7 Positive skin prick test to egg at 18 months	2	335	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.52, 1.74]
8 Positive skin prick test to milk at 6 months	2	340	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.29, 4.51]
9 Positive skin prick test to milk at 18 months	2	335	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.16, 4.59]
10 Detectable cord blood IgE (\geq .125 U/ml)	2	287	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.94, 1.44]
11 Cord blood IgE > 1 U/ml	1	91	Risk Ratio (M-H, Fixed, 95% CI)	2.81 [1.00, 7.90]
12 Preterm birth	2	236	Risk Ratio (M-H, Random, 95% CI)	10.06 [0.53, 192.26]
13 Gestational weight gain (as % of prepregnancy weight)	1	164	Mean Difference (IV, Fixed, 95% CI)	-3.0 [-5.21, -0.79]
14 Birthweight (g)	2	236	Mean Difference (IV, Random, 95% CI)	-83.45 [-221.87, 54.97]

Comparison 2. Maternal antigen avoidance during lactation in women at high risk for atopic offspring

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incidence of atopic eczema in first 18 months	1	26	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.32, 1.64]
2 Positive skin prick test to milk at 1 year	1	497	Risk Ratio (M-H, Fixed, 95% CI)	1.43 [0.68, 3.01]
3 Positive skin prick test to egg at 1 year	1	497	Risk Ratio (M-H, Fixed, 95% CI)	1.31 [0.88, 1.94]
4 Positive skin prick test to peanut at 1 year	1	497	Risk Ratio (M-H, Fixed, 95% CI)	1.41 [0.76, 2.60]

5 Positive skin prick test to milk at 2 years	1	473	Risk Ratio (M-H, Fixed, 95% CI)	4.30 [0.94, 19.67]
6 Positive skin prick test to egg at 2 years	1	473	Risk Ratio (M-H, Fixed, 95% CI)	1.91 [1.03, 3.53]
7 Positive skin prick test to peanut at 2 years	1	473	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.56, 1.80]
8 Positive skin prick test to milk at 7 years	1	354	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.13, 6.41]
9 Positive skin prick test to egg at 7 years	1	354	Risk Ratio (M-H, Fixed, 95% CI)	0.15 [0.02, 1.25]
10 Positive skin prick test to peanut at 7 years	1	354	Risk Ratio (M-H, Fixed, 95% CI)	1.60 [0.81, 3.15]

Comparison 3. Maternal antigen avoidance during lactation for treating atopic eczema in infants

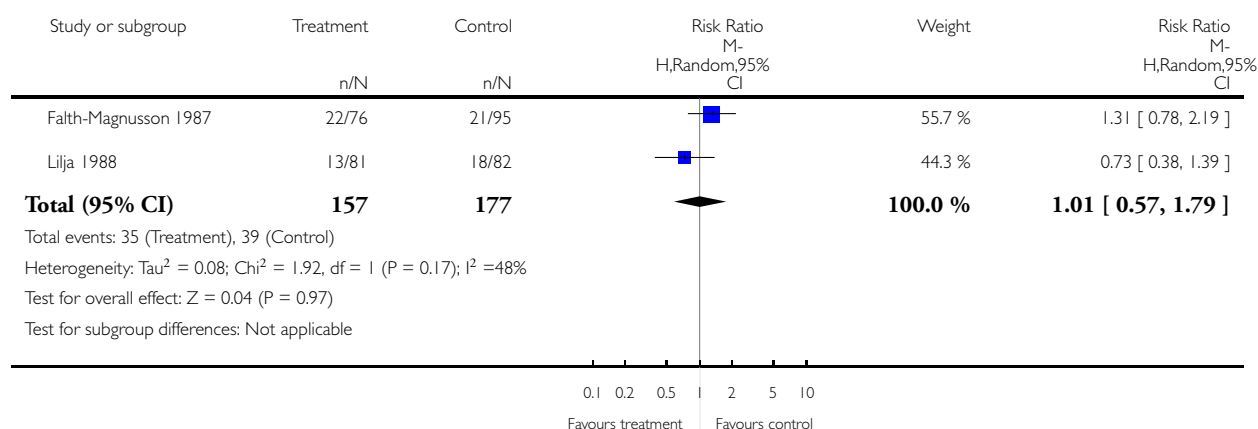
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Eczema area score	1	34	Mean Difference (IV, Fixed, 95% CI)	-0.80 [-4.43, 2.83]
2 Eczema activity score	1	34	Mean Difference (IV, Fixed, 95% CI)	-1.40 [-7.18, 4.38]

Analysis 1.1. Comparison 1 Maternal antigen avoidance in pregnancy in women at high risk for atopic offspring, Outcome 1 Atopic eczema in first 12-18 months.

Review: Maternal dietary antigen avoidance during pregnancy or lactation, or both, for preventing or treating atopic disease in the child

Comparison: 1 Maternal antigen avoidance in pregnancy in women at high risk for atopic offspring

Outcome: 1 Atopic eczema in first 12-18 months

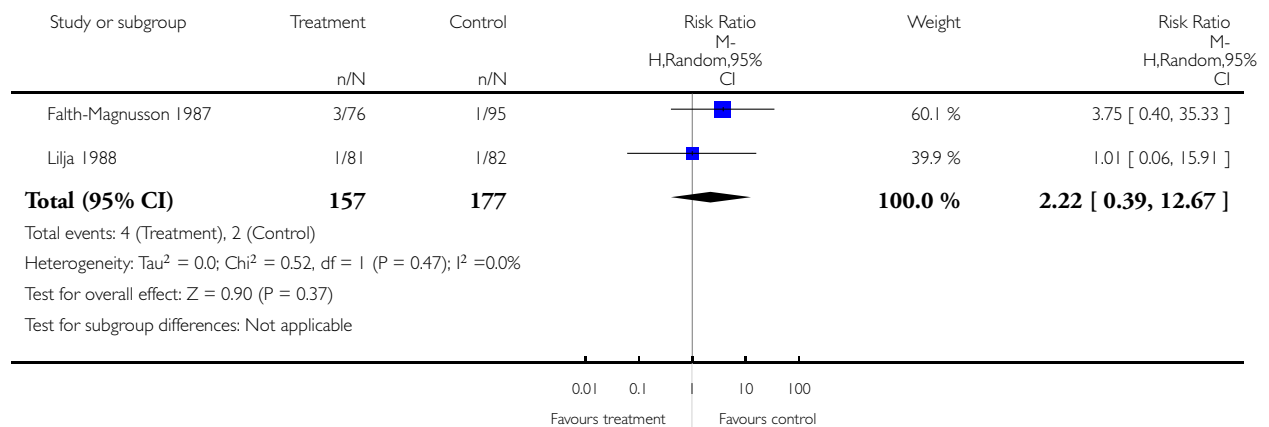


Analysis 1.2. Comparison 1 Maternal antigen avoidance in pregnancy in women at high risk for atopic offspring, Outcome 2 Asthma in first 18 months.

Review: Maternal dietary antigen avoidance during pregnancy or lactation, or both, for preventing or treating atopic disease in the child

Comparison: 1 Maternal antigen avoidance in pregnancy in women at high risk for atopic offspring

Outcome: 2 Asthma in first 18 months

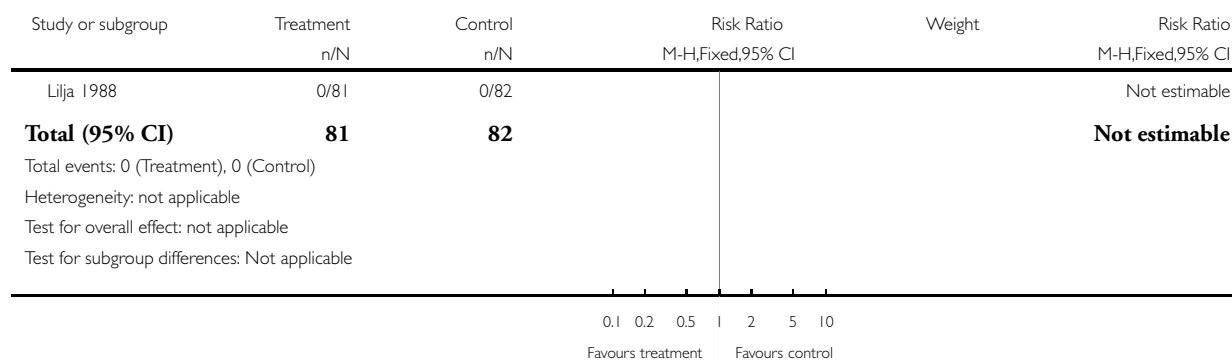


Analysis 1.3. Comparison 1 Maternal antigen avoidance in pregnancy in women at high risk for atopic offspring, Outcome 3 Allergic rhinitis/conjunctivitis in first 18 months.

Review: Maternal dietary antigen avoidance during pregnancy or lactation, or both, for preventing or treating atopic disease in the child

Comparison: 1 Maternal antigen avoidance in pregnancy in women at high risk for atopic offspring

Outcome: 3 Allergic rhinitis/conjunctivitis in first 18 months

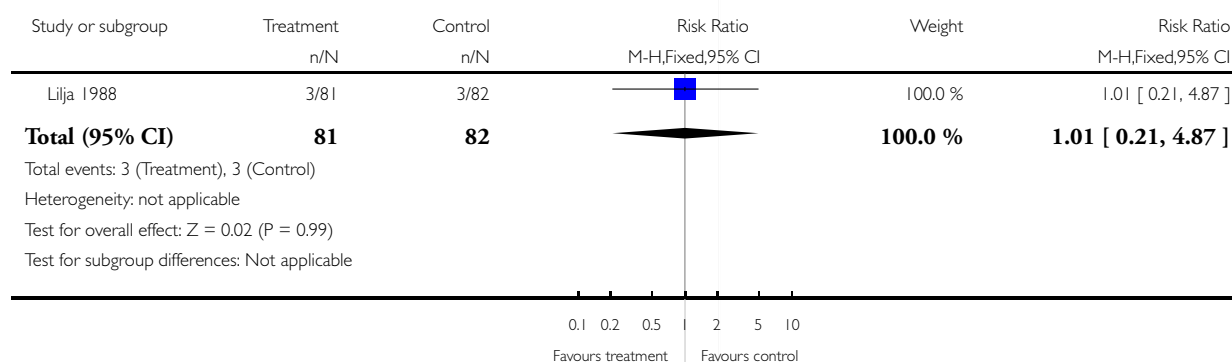


Analysis 1.4. Comparison 1 Maternal antigen avoidance in pregnancy in women at high risk for atopic offspring, Outcome 4 Allergic urticaria in first 18 months.

Review: Maternal dietary antigen avoidance during pregnancy or lactation, or both, for preventing or treating atopic disease in the child

Comparison: 1 Maternal antigen avoidance in pregnancy in women at high risk for atopic offspring

Outcome: 4 Allergic urticaria in first 18 months

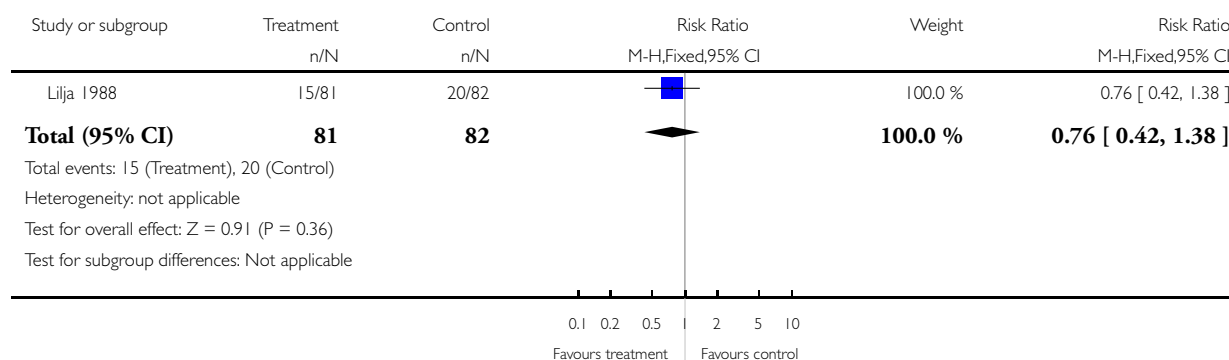


Analysis 1.5. Comparison 1 Maternal antigen avoidance in pregnancy in women at high risk for atopic offspring, Outcome 5 Any atopic condition in first 18 months.

Review: Maternal dietary antigen avoidance during pregnancy or lactation, or both, for preventing or treating atopic disease in the child

Comparison: 1 Maternal antigen avoidance in pregnancy in women at high risk for atopic offspring

Outcome: 5 Any atopic condition in first 18 months

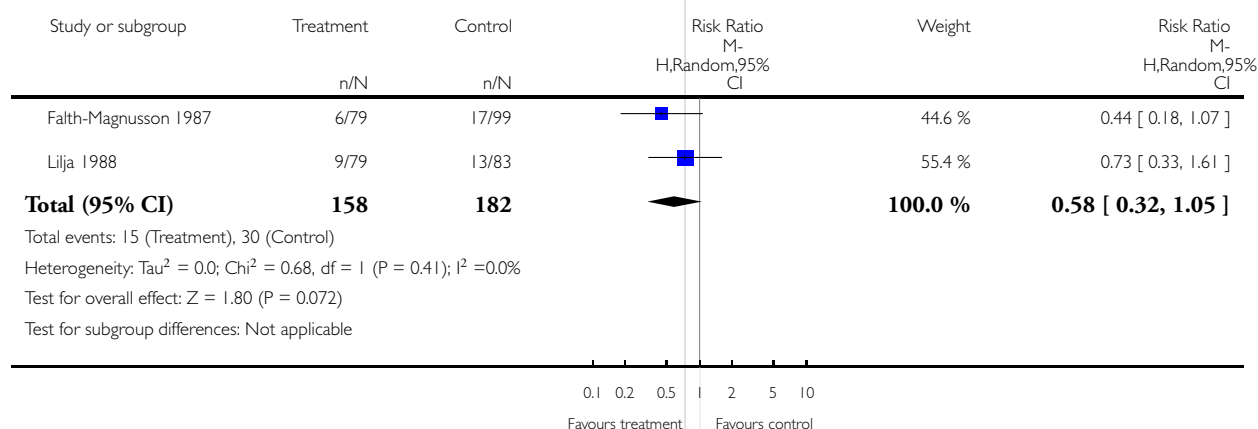


Analysis 1.6. Comparison 1 Maternal antigen avoidance in pregnancy in women at high risk for atopic offspring, Outcome 6 Positive skin prick test to egg at 6 months.

Review: Maternal dietary antigen avoidance during pregnancy or lactation, or both, for preventing or treating atopic disease in the child

Comparison: 1 Maternal antigen avoidance in pregnancy in women at high risk for atopic offspring

Outcome: 6 Positive skin prick test to egg at 6 months

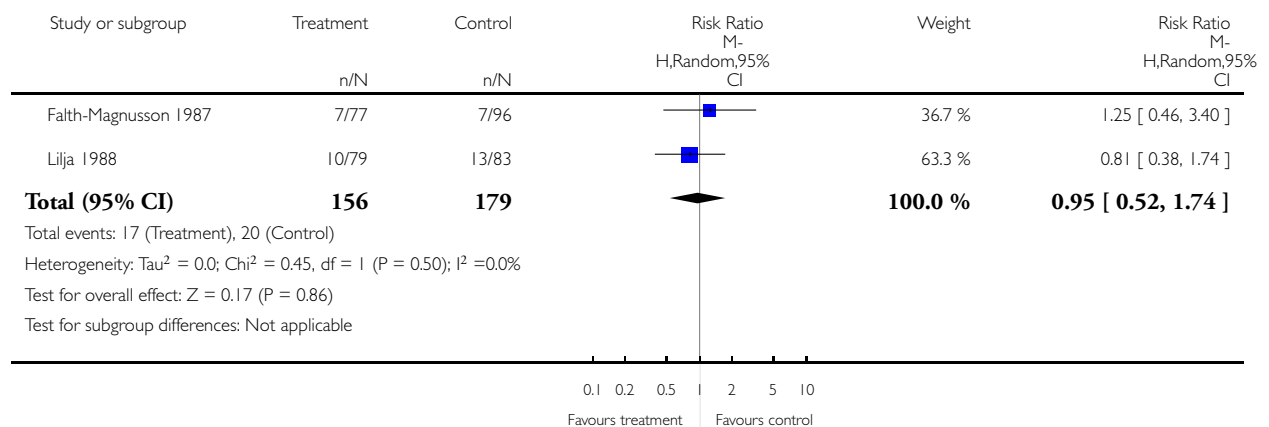


Analysis 1.7. Comparison 1 Maternal antigen avoidance in pregnancy in women at high risk for atopic offspring, Outcome 7 Positive skin prick test to egg at 18 months.

Review: Maternal dietary antigen avoidance during pregnancy or lactation, or both, for preventing or treating atopic disease in the child

Comparison: 1 Maternal antigen avoidance in pregnancy in women at high risk for atopic offspring

Outcome: 7 Positive skin prick test to egg at 18 months

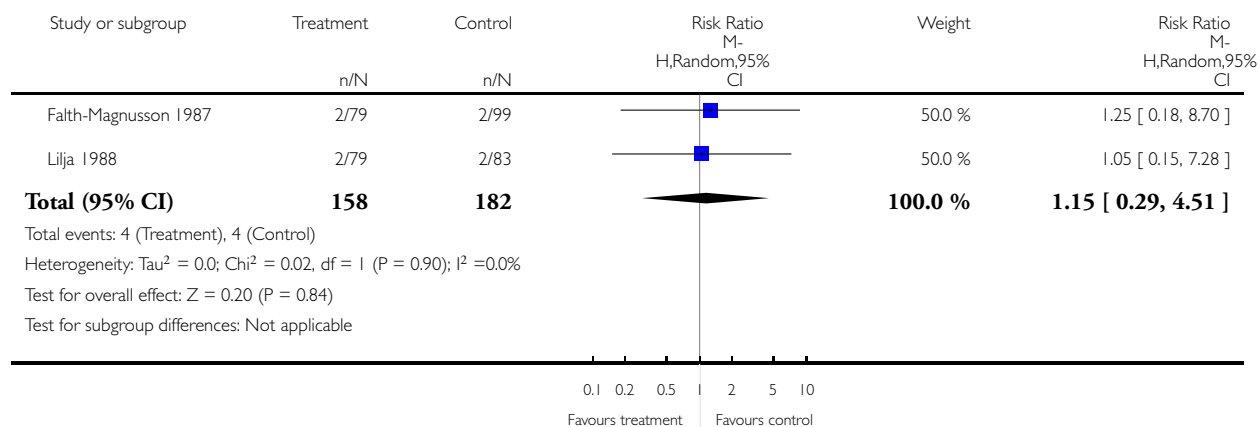


Analysis 1.8. Comparison 1 Maternal antigen avoidance in pregnancy in women at high risk for atopic offspring, Outcome 8 Positive skin prick test to milk at 6 months.

Review: Maternal dietary antigen avoidance during pregnancy or lactation, or both, for preventing or treating atopic disease in the child

Comparison: 1 Maternal antigen avoidance in pregnancy in women at high risk for atopic offspring

Outcome: 8 Positive skin prick test to milk at 6 months

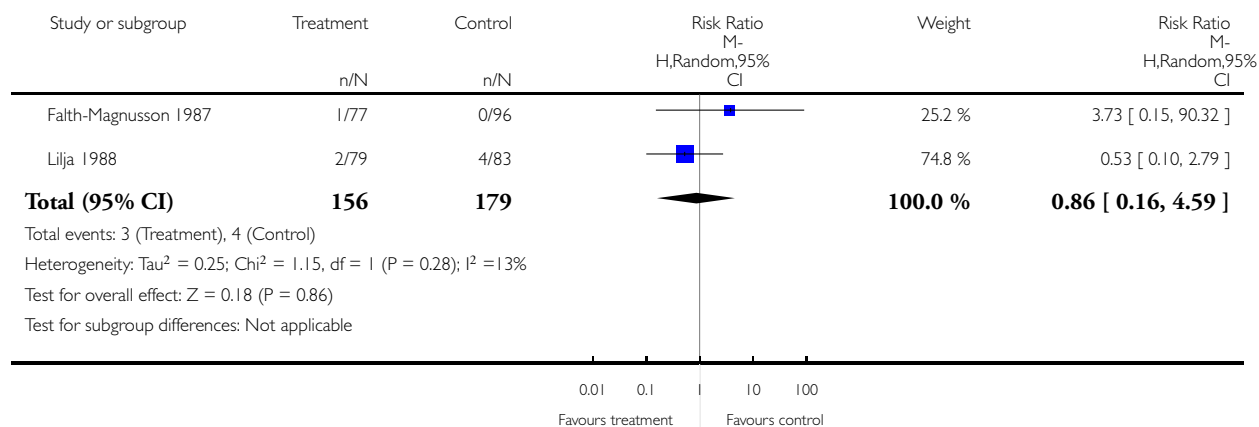


Analysis 1.9. Comparison 1 Maternal antigen avoidance in pregnancy in women at high risk for atopic offspring, Outcome 9 Positive skin prick test to milk at 18 months.

Review: Maternal dietary antigen avoidance during pregnancy or lactation, or both, for preventing or treating atopic disease in the child

Comparison: 1 Maternal antigen avoidance in pregnancy in women at high risk for atopic offspring

Outcome: 9 Positive skin prick test to milk at 18 months

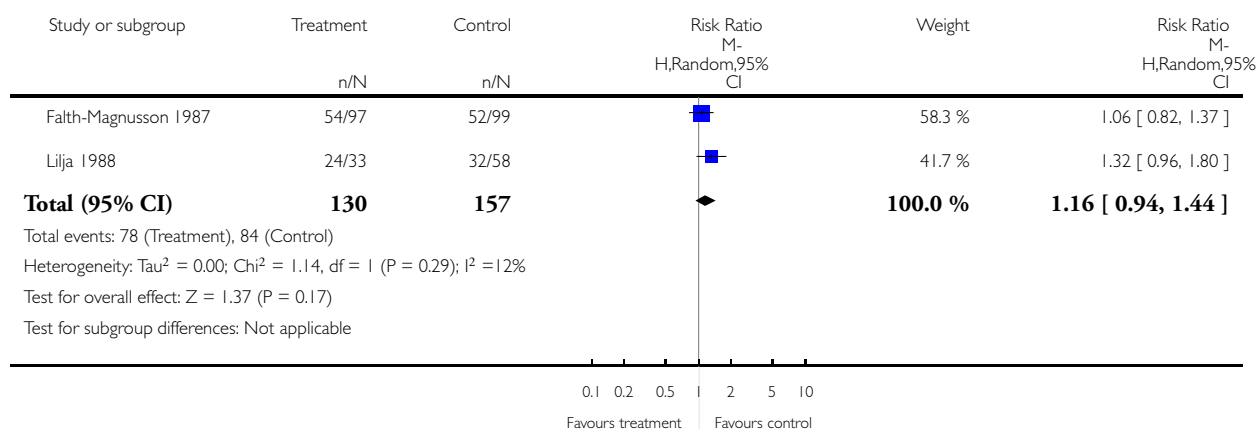


Analysis 1.10. Comparison 1 Maternal antigen avoidance in pregnancy in women at high risk for atopic offspring, Outcome 10 Detectable cord blood IgE ($\geq .125$ U/ml).

Review: Maternal dietary antigen avoidance during pregnancy or lactation, or both, for preventing or treating atopic disease in the child

Comparison: 1 Maternal antigen avoidance in pregnancy in women at high risk for atopic offspring

Outcome: 10 Detectable cord blood IgE ($\geq .125$ U/ml)

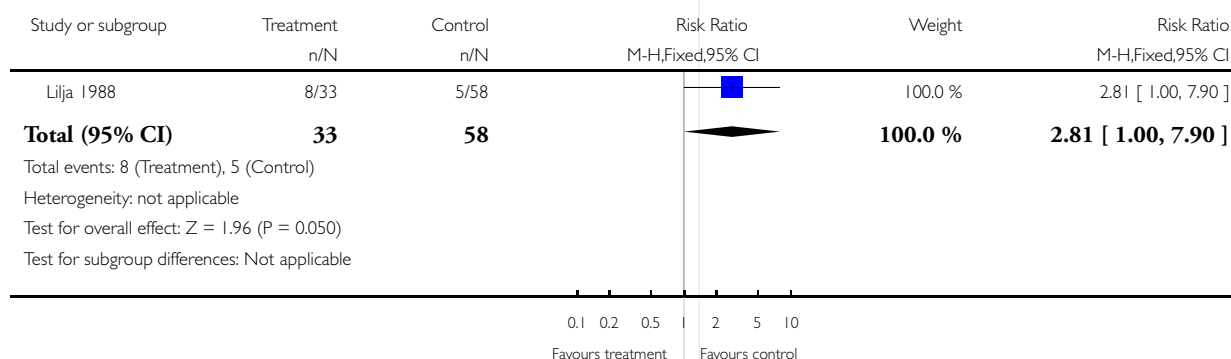


Analysis 1.11. Comparison 1 Maternal antigen avoidance in pregnancy in women at high risk for atopic offspring, Outcome 11 Cord blood IgE > 1 U/ml.

Review: Maternal dietary antigen avoidance during pregnancy or lactation, or both, for preventing or treating atopic disease in the child

Comparison: 1 Maternal antigen avoidance in pregnancy in women at high risk for atopic offspring

Outcome: 11 Cord blood IgE > 1 U/ml

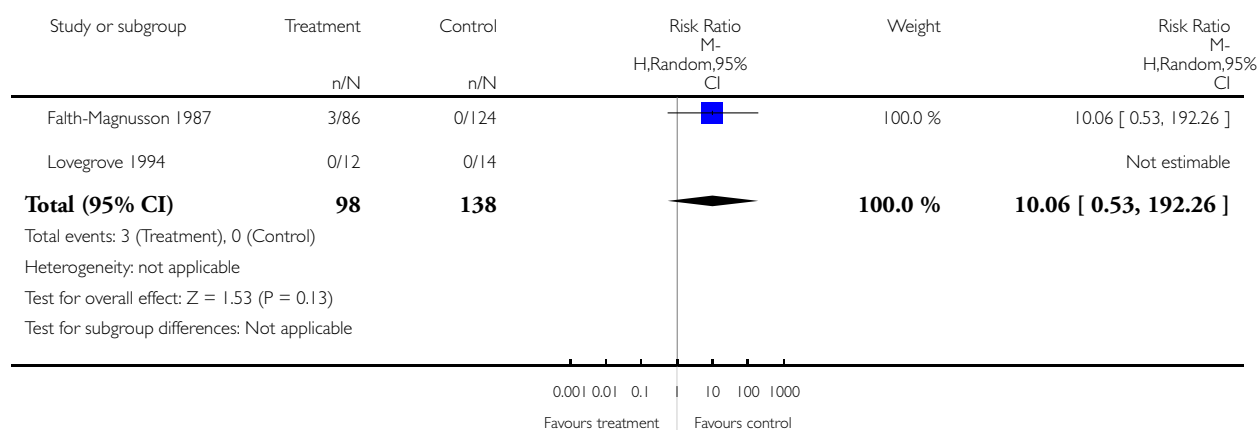


Analysis 1.12. Comparison 1 Maternal antigen avoidance in pregnancy in women at high risk for atopic offspring, Outcome 12 Preterm birth.

Review: Maternal dietary antigen avoidance during pregnancy or lactation, or both, for preventing or treating atopic disease in the child

Comparison: 1 Maternal antigen avoidance in pregnancy in women at high risk for atopic offspring

Outcome: 12 Preterm birth

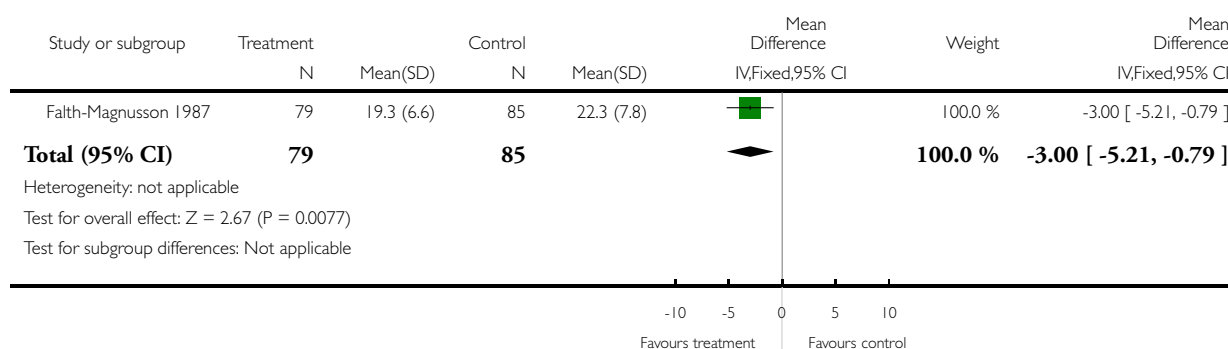


Analysis 1.13. Comparison 1 Maternal antigen avoidance in pregnancy in women at high risk for atopic offspring, Outcome 13 Gestational weight gain (as % of prepregnancy weight).

Review: Maternal dietary antigen avoidance during pregnancy or lactation, or both, for preventing or treating atopic disease in the child

Comparison: 1 Maternal antigen avoidance in pregnancy in women at high risk for atopic offspring

Outcome: 13 Gestational weight gain (as % of prepregnancy weight)

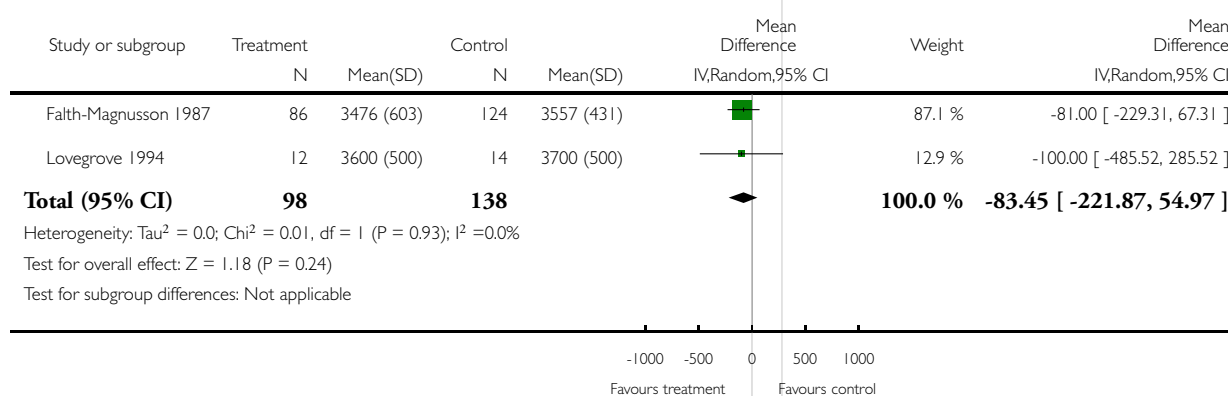


Analysis 1.14. Comparison 1 Maternal antigen avoidance in pregnancy in women at high risk for atopic offspring, Outcome 14 Birthweight (g).

Review: Maternal dietary antigen avoidance during pregnancy or lactation, or both, for preventing or treating atopic disease in the child

Comparison: 1 Maternal antigen avoidance in pregnancy in women at high risk for atopic offspring

Outcome: 14 Birthweight (g)

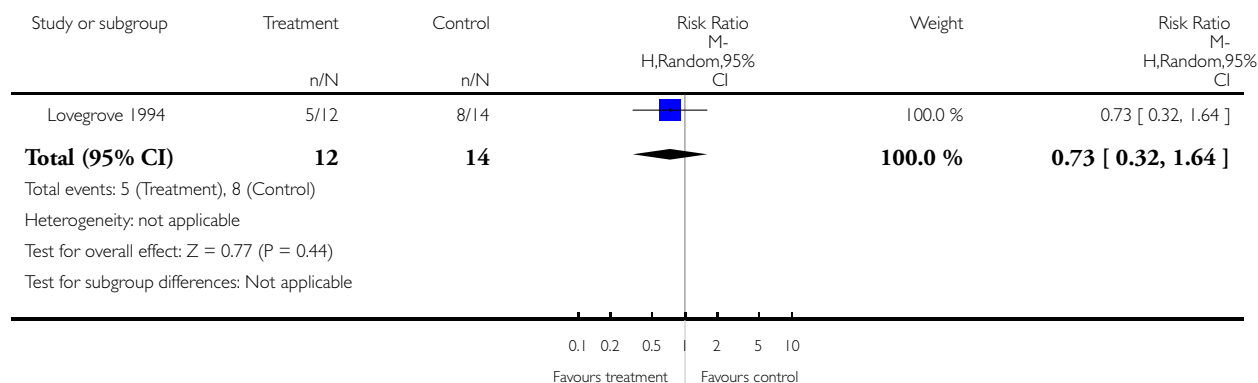


Analysis 2.1. Comparison 2 Maternal antigen avoidance during lactation in women at high risk for atopic offspring, Outcome 1 Incidence of atopic eczema in first 18 months.

Review: Maternal dietary antigen avoidance during pregnancy or lactation, or both, for preventing or treating atopic disease in the child

Comparison: 2 Maternal antigen avoidance during lactation in women at high risk for atopic offspring

Outcome: 1 Incidence of atopic eczema in first 18 months

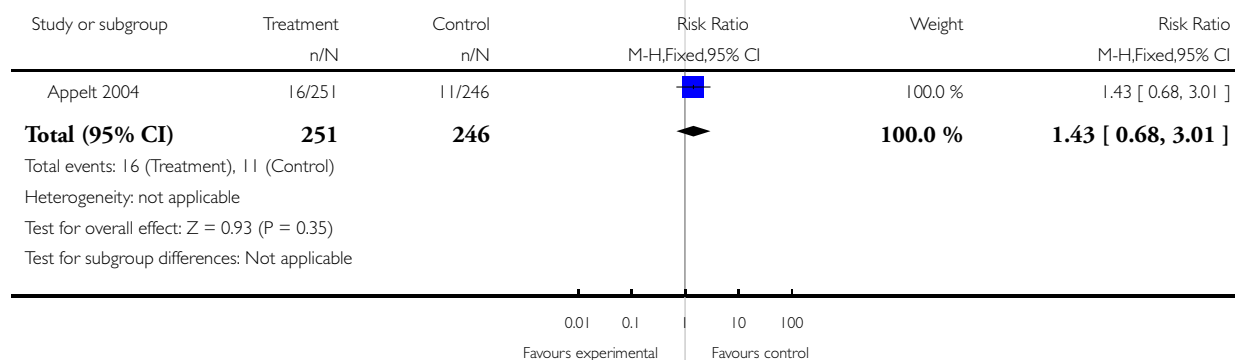


Analysis 2.2. Comparison 2 Maternal antigen avoidance during lactation in women at high risk for atopic offspring, Outcome 2 Positive skin prick test to milk at 1 year.

Review: Maternal dietary antigen avoidance during pregnancy or lactation, or both, for preventing or treating atopic disease in the child

Comparison: 2 Maternal antigen avoidance during lactation in women at high risk for atopic offspring

Outcome: 2 Positive skin prick test to milk at 1 year

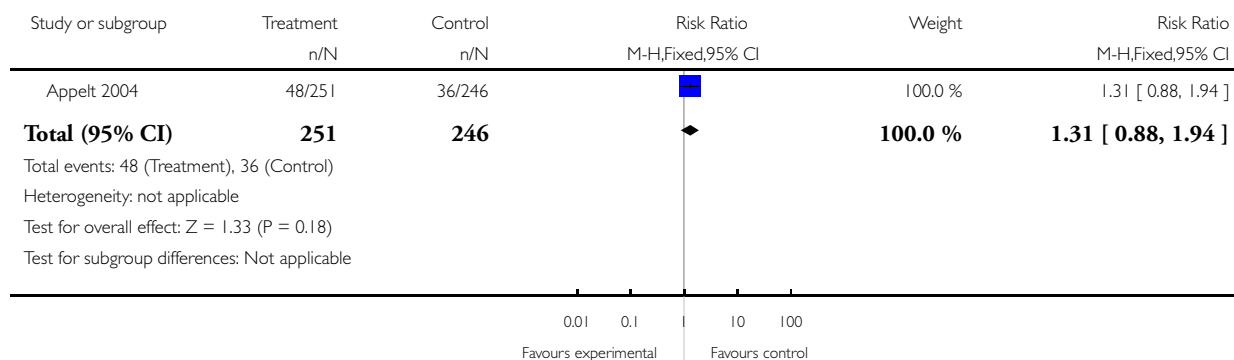


Analysis 2.3. Comparison 2 Maternal antigen avoidance during lactation in women at high risk for atopic offspring, Outcome 3 Positive skin prick test to egg at 1 year.

Review: Maternal dietary antigen avoidance during pregnancy or lactation, or both, for preventing or treating atopic disease in the child

Comparison: 2 Maternal antigen avoidance during lactation in women at high risk for atopic offspring

Outcome: 3 Positive skin prick test to egg at 1 year

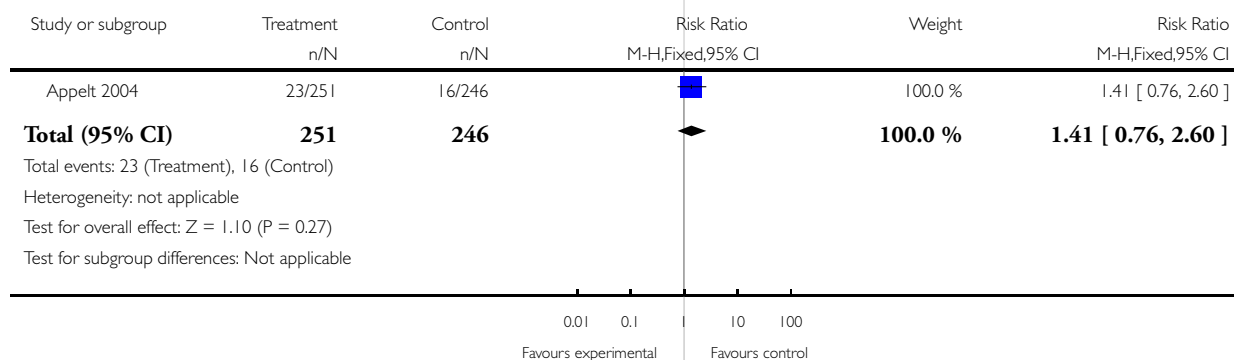


Analysis 2.4. Comparison 2 Maternal antigen avoidance during lactation in women at high risk for atopic offspring, Outcome 4 Positive skin prick test to peanut at 1 year.

Review: Maternal dietary antigen avoidance during pregnancy or lactation, or both, for preventing or treating atopic disease in the child

Comparison: 2 Maternal antigen avoidance during lactation in women at high risk for atopic offspring

Outcome: 4 Positive skin prick test to peanut at 1 year

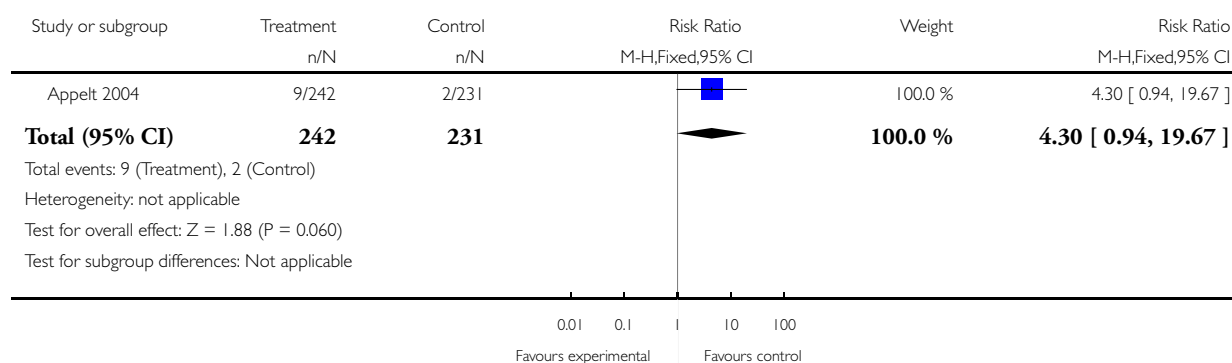


Analysis 2.5. Comparison 2 Maternal antigen avoidance during lactation in women at high risk for atopic offspring, Outcome 5 Positive skin prick test to milk at 2 years.

Review: Maternal dietary antigen avoidance during pregnancy or lactation, or both, for preventing or treating atopic disease in the child

Comparison: 2 Maternal antigen avoidance during lactation in women at high risk for atopic offspring

Outcome: 5 Positive skin prick test to milk at 2 years

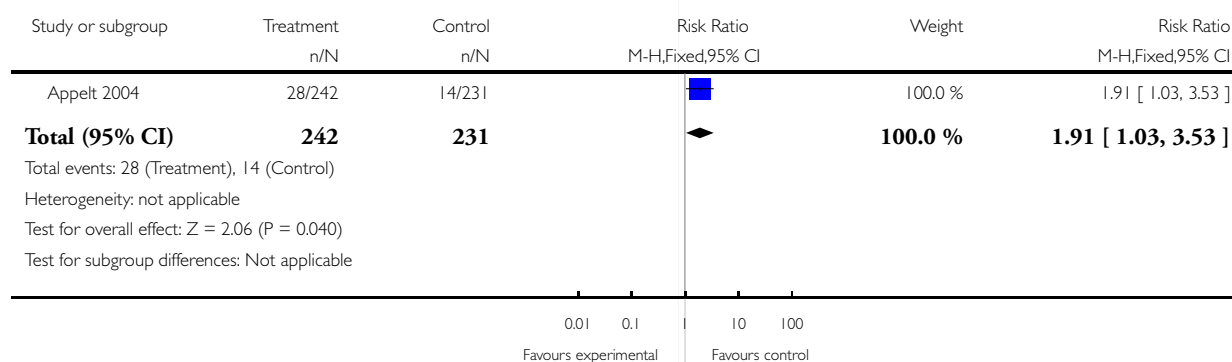


Analysis 2.6. Comparison 2 Maternal antigen avoidance during lactation in women at high risk for atopic offspring, Outcome 6 Positive skin prick test to egg at 2 years.

Review: Maternal dietary antigen avoidance during pregnancy or lactation, or both, for preventing or treating atopic disease in the child

Comparison: 2 Maternal antigen avoidance during lactation in women at high risk for atopic offspring

Outcome: 6 Positive skin prick test to egg at 2 years

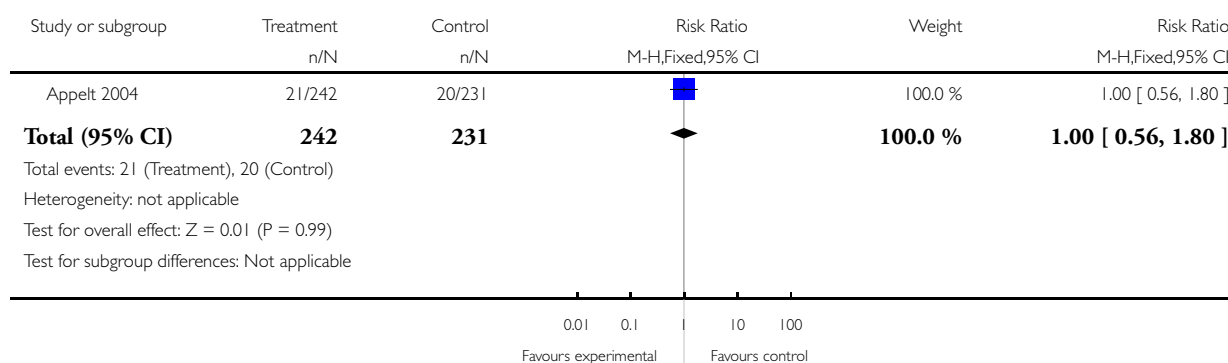


Analysis 2.7. Comparison 2 Maternal antigen avoidance during lactation in women at high risk for atopic offspring, Outcome 7 Positive skin prick test to peanut at 2 years.

Review: Maternal dietary antigen avoidance during pregnancy or lactation, or both, for preventing or treating atopic disease in the child

Comparison: 2 Maternal antigen avoidance during lactation in women at high risk for atopic offspring

Outcome: 7 Positive skin prick test to peanut at 2 years

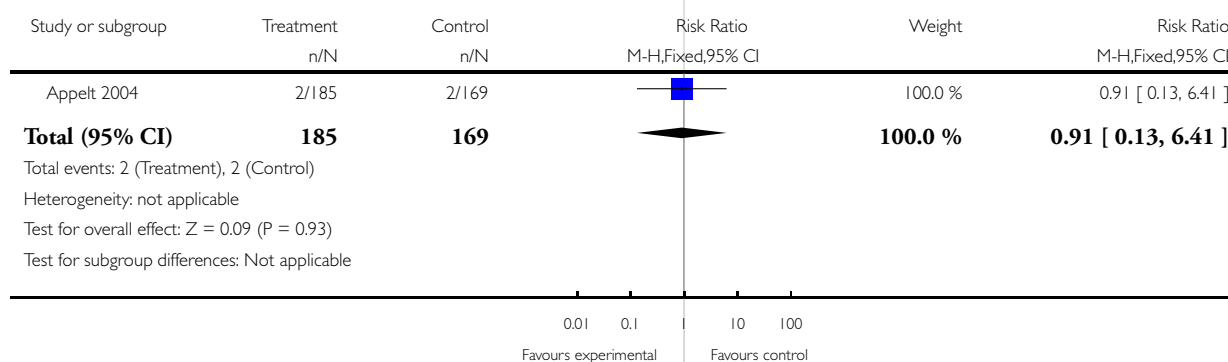


Analysis 2.8. Comparison 2 Maternal antigen avoidance during lactation in women at high risk for atopic offspring, Outcome 8 Positive skin prick test to milk at 7 years.

Review: Maternal dietary antigen avoidance during pregnancy or lactation, or both, for preventing or treating atopic disease in the child

Comparison: 2 Maternal antigen avoidance during lactation in women at high risk for atopic offspring

Outcome: 8 Positive skin prick test to milk at 7 years

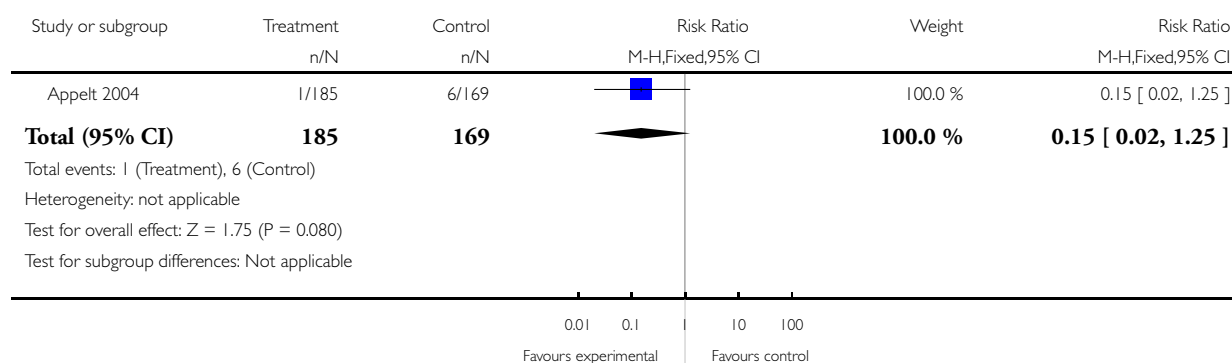


Analysis 2.9. Comparison 2 Maternal antigen avoidance during lactation in women at high risk for atopic offspring, Outcome 9 Positive skin prick test to egg at 7 years.

Review: Maternal dietary antigen avoidance during pregnancy or lactation, or both, for preventing or treating atopic disease in the child

Comparison: 2 Maternal antigen avoidance during lactation in women at high risk for atopic offspring

Outcome: 9 Positive skin prick test to egg at 7 years

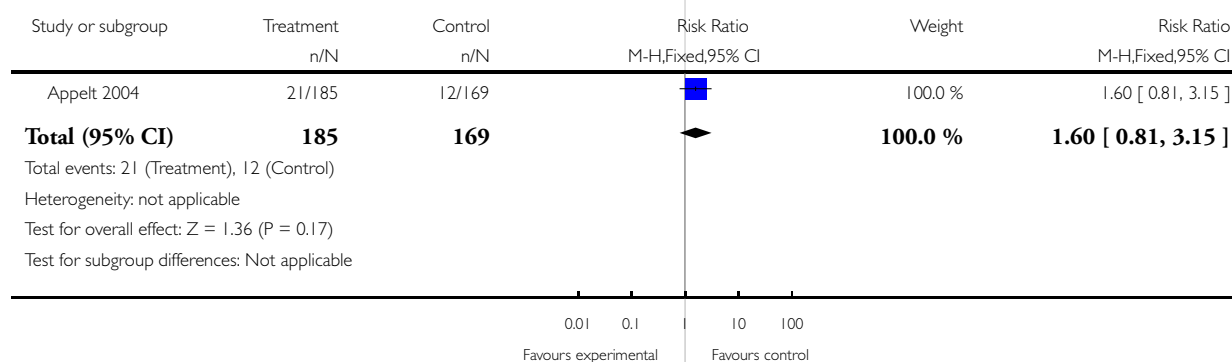


Analysis 2.10. Comparison 2 Maternal antigen avoidance during lactation in women at high risk for atopic offspring, Outcome 10 Positive skin prick test to peanut at 7 years.

Review: Maternal dietary antigen avoidance during pregnancy or lactation, or both, for preventing or treating atopic disease in the child

Comparison: 2 Maternal antigen avoidance during lactation in women at high risk for atopic offspring

Outcome: 10 Positive skin prick test to peanut at 7 years

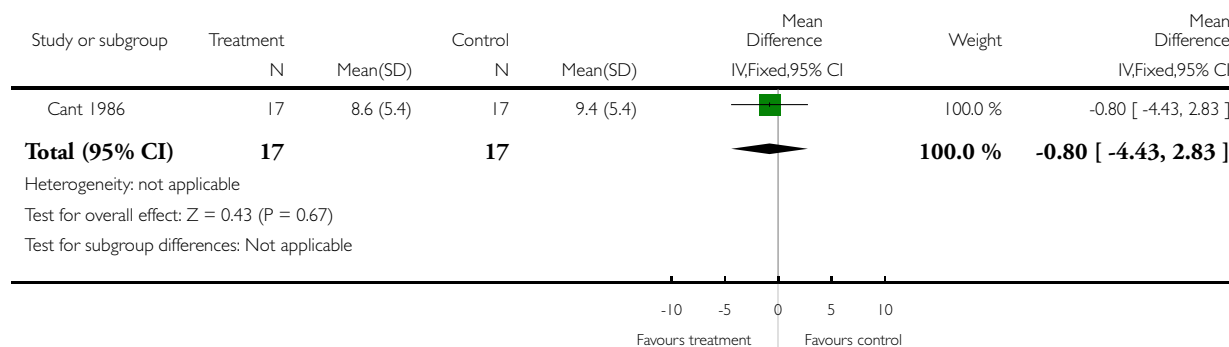


Analysis 3.1. Comparison 3 Maternal antigen avoidance during lactation for treating atopic eczema in infants, Outcome 1 Eczema area score.

Review: Maternal dietary antigen avoidance during pregnancy or lactation, or both, for preventing or treating atopic disease in the child

Comparison: 3 Maternal antigen avoidance during lactation for treating atopic eczema in infants

Outcome: 1 Eczema area score

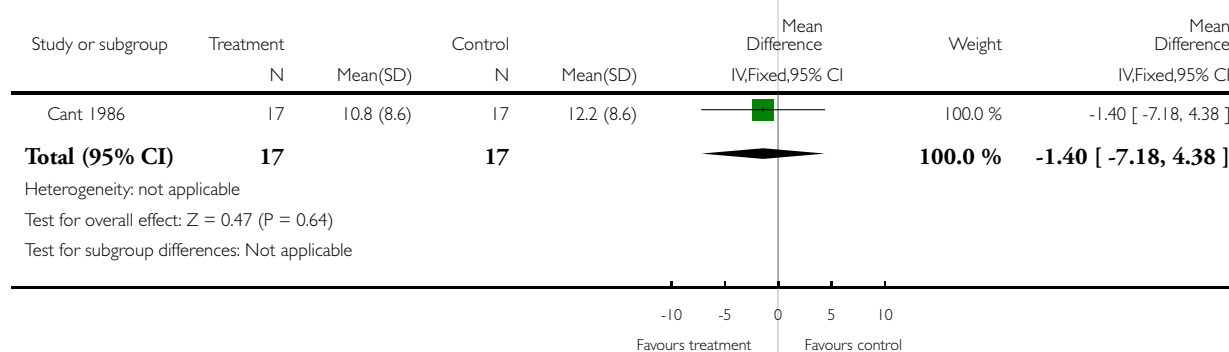


Analysis 3.2. Comparison 3 Maternal antigen avoidance during lactation for treating atopic eczema in infants, Outcome 2 Eczema activity score.

Review: Maternal dietary antigen avoidance during pregnancy or lactation, or both, for preventing or treating atopic disease in the child

Comparison: 3 Maternal antigen avoidance during lactation for treating atopic eczema in infants

Outcome: 2 Eczema activity score



APPENDICES

Appendix I. Methods used in previous version

Two review authors independently evaluated trials under consideration for methodological quality and appropriateness for inclusion, without consideration of their results. We processed included trial data as described in the *Cochrane Reviewers' Handbook* (Clarke 2003). We have not included Appelt 2004 and Lovegrove 1994 in the comparison of atopic outcomes for dietary antigen avoidance during pregnancy, because the intervention continued into lactation.

We have excluded from this update two trials by Chandra et al (Chandra 1986; Chandra 1989) included in the original versions of this review because of evidence that the published data may have been fabricated.

Because of the small sample sizes of trials and large differences in the control rates of atopic outcomes, all pooled effect estimates are derived from random-effects models even in the absence of statistically significant heterogeneity in the results of the pooled trials.

WHAT'S NEW

Last assessed as up-to-date: 23 July 2012.

Date	Event	Description
9 July 2012	New citation required but conclusions have not changed	Review updated with a new search.
6 July 2012	New search has been performed	Search updated. No new trial reports identified.

HISTORY

Protocol first published: Issue 2, 1996

Review first published: Issue 2, 1996

Date	Event	Description
30 April 2011	New search has been performed	Search updated. Three new trials identified; one included (Appelt 2004) and two excluded (Arshad 2007; Vance 2004).
17 September 2008	Amended	Converted to new review format.
29 April 2006	New search has been performed	Search updated. Two new trial reports added to 'Studies awaiting assessment.' One new report added to Falth-Magnusson 1987 (included study) and another added to Arshad 1992 (excluded).
29 April 2006	New citation required but conclusions have not changed	We have excluded two trials by Chandra et al (Chandra 1986; Chandra 1989) included in previous versions of this review because of evidence that the published data may have been fabricated. The exclusion of these

(Continued)

		trials does not change the conclusions of the review. However, the earlier version of this review suggested that there may be a possibility of benefit with antigen avoidance during lactation. In this update, with the exclusion of the two trials reporting data of uncertain veracity, the evidence is insufficient to infer that antigen avoidance during lactation is beneficial or harmful
1 October 2002	New search has been performed	<p>This updated review combines and replaces three previously published Cochrane reviews:</p> <p>(1) 'Maternal antigen avoidance during pregnancy and/or lactation for preventing or treating atopic disease in the child' (CDSR 2003a);</p> <p>(2) 'Maternal antigen avoidance during lactation for preventing atopic eczema in infants' (Kramer 1996a);</p> <p>(3) 'Maternal antigen avoidance during lactation for preventing atopic disease in infants of women at high risk' (Kramer 1996b).</p> <p>This combination was suggested by colleagues in the field, by the PCG editors, and by the Cochrane Pregnancy and Childbirth Group's Consumer Panel</p>

CONTRIBUTIONS OF AUTHORS

M Kramer developed the three original separate reviews that have been combined in this updated amalgamation. R Kakuma carried out independent quality rating and data extraction of all included studies and helped revise the [Characteristics of included studies](#) table. M Kramer updated the review in April 2011.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- McGill University, Canada.

External sources

- Canadian Institutes of Health Research, Canada.

INDEX TERMS

Medical Subject Headings (MeSH)

*Diet, Protein-Restricted; *Lactation; Allergens [*adverse effects]; Dermatitis, Atopic [prevention & control]; Dietary Proteins [*adverse effects]; Food Hypersensitivity; Hypersensitivity, Immediate [*prevention & control]; Randomized Controlled Trials as Topic; Risk Factors

MeSH check words

Female; Humans; Infant; Infant, Newborn; Pregnancy