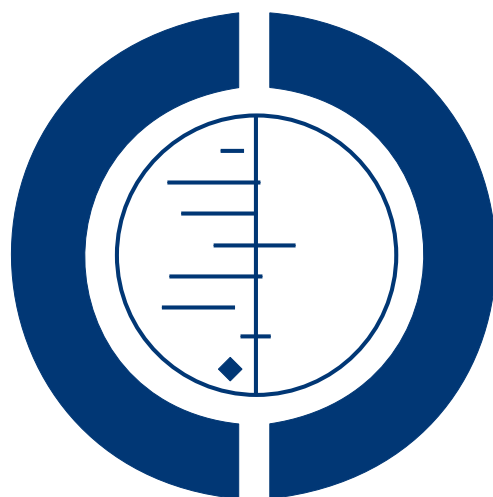


Mono and multifaceted inhalant and/or food allergen reduction interventions for preventing asthma in children at high risk of developing asthma (Review)

Maas T, Kaper J, Sheikh A, Knottnerus JA, Wesseling G, Dompeling E, Muris JWM, van Schayck CP



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[Intervention Review]

Mono and multifaceted inhalant and/or food allergen reduction interventions for preventing asthma in children at high risk of developing asthma

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ABSTRACT

Background

Allergen exposure is one of the environmental factors seemingly associated with the development of asthma. If asthma is a multi-factorial disease, it is hypothesised that prevention might only prove effective if most or all relevant environmental factors are simultaneously avoided.

Objectives

To assess effect(s) of monofaceted and multifaceted interventions compared with control interventions in preventing asthma and asthma symptoms in high risk children.

Search strategy

We searched the Cochrane Airways Trials Register (December 2008).

Selection criteria

Randomised controlled trials of allergen exposure reduction for the primary prevention of asthma in children. Interventions were multifaceted (reducing exposure to both inhalant and food allergens) or monofaceted (reducing exposure to either inhalant or food allergens) Follow up had to be from birth (or during pregnancy) up to a minimum of two years of age.

Data collection and analysis

Mono and multifaceted inhalant and/or food allergen reduction interventions for preventing asthma in children at high risk of developing asthma (Review) |

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We included in the analysis studies assessing the primary outcome (current diagnosis: asthma) and/or one of the secondary outcomes (current respiratory symptoms: wheezing, nocturnal coughing and dyspnoea). We pooled multifaceted and monofaceted intervention trials separately. We made an indirect comparison of their effects using tests for interaction to calculate relative odds ratios.

Main results

We included three multifaceted and six monofaceted intervention studies (3271 children). Physician diagnosed asthma in children less than five years, and asthma as defined by respiratory symptoms and lung function criteria in children aged five years and older, both favoured treatment with a multifaceted intervention compared to usual care (< 5 years: odds ratio (OR) 0.72, 95% confidence interval (CI) 0.54 to 0.96, and > 5 years: OR 0.52, 95% CI 0.32 to 0.85). However, there was no significant difference in outcome between monofaceted intervention and control interventions (< 5 years: OR 1.12, 95% CI 0.76 to 1.64, and > 5 years: OR 0.83, 95% CI 0.59 to 1.16). Indirect comparison between these treatments did not demonstrate a significant difference between multiple interventions and mono-interventions in reducing the frequency of asthma diagnosis in children under five years (relative OR 0.64 (95% CI 0.40 to 1.04, $P = 0.07$) or five years and older (relative OR 0.63, 95% CI 0.35 to 1.13, $P = 0.12$). There was also no significant difference between either mono- and multifaceted intervention and control in reducing the likelihood of symptoms of nocturnal coughing at follow up. Wheezing, however, showed a significant difference between multifaceted and mono-interventions (relative OR 0.59, 95% CI 0.35 to 0.99, $P = 0.04$), but the significance was lost when data on treatment only was analysed.

Authors' conclusions

The available evidence suggests that the reduction of exposure to multiple allergens compared to usual care reduces the likelihood of a current diagnosis of asthma in children (at ages < 5 years and 5 years and older). Mono-intervention studies have not produced effects which are statistically significant compared with control. In children who are at risk of developing childhood asthma, multifaceted interventions, characterised by dietary allergen reduction and environmental remediation, reduce the odds of a physician diagnosis of asthma later in childhood by half. This translates to a number needed to treat (NNT) of 17. The effect of multi-faceted interventions on parent reported wheeze was inconsistent and had no significant impact on nocturnal coughing or dyspnoea. Data from monofaceted intervention exposed children studies were not significantly different from those of control groups for all outcomes. There remains uncertainty as to whether multiple interventions are more effective than mono-component interventions. The comparisons made were indirect, making the conclusions drawn uncertain. To our knowledge there are no ongoing studies in which both intervention strategies are randomly compared. The findings, however, warrant further direct comparison between multiple- and monofaceted interventions aimed at reducing the prevalence of asthma in children.

PLAIN LANGUAGE SUMMARY

Mono and multifaceted allergen reducing interventions for the primary prevention of asthma in children at high risk of developing asthma

It is possible that early exposure to allergens (substances which cause allergy) may lead to development of asthma in high risk children. This review asks whether the risk of developing asthma, which is a disease caused by many factors, can be decreased by reducing single allergen levels in children with genetic susceptibility, or whether the reduction of more than one type of allergen exposure simultaneously will lead to a better outcome. As a direct comparison could not be made using current research we made indirect comparisons using trials that had compared single or multiple interventions with a control. In children who are at risk of developing childhood asthma 'multifaceted' interventions, which involve both dietary allergen reduction and environmental change to reduce exposure to inhaled allergens, reduce the odds of a doctor diagnosing asthma later in childhood by half. However, the effect of these multifaceted interventions on wheeze reported by parents was inconsistent and there was no beneficial effect on night-time coughing or breathlessness. Single ('monofaceted') interventions were not significantly more effective than controls in the reduction of all outcomes, but there remains uncertainty as to whether multiple interventions are more effective than single component interventions.

BACKGROUND

Asthma is a multi-factorial disease that, in the main, develops in individuals with genetic susceptibility. Genetically predisposed

children exposed to specific environmental factors (such as allergens) are believed to be at increased risk of developing asthma. It is generally accepted that the interaction between genotype and environment plays a crucial role (Martinez 1997). In this line of thinking it is assumed that reduction of exposure to allergens (inhalant as well as food allergens) could lead to a reduction in the risk of developing asthma, although current evidence on maternal dietary antigen avoidance is equivocal (Kramer 2006). Information leading to the assumption that reducing exposure to one type of allergen might not be effective is based on results of secondary prevention strategies (Boner 1985; Platts-Mills 1982). Many have speculated that reduction of exposure to inhalant or food allergens could lead to a reduction in the risk of developing asthma. It has, however, proven very difficult to translate these insights into effective primary prevention strategies (Gøtzsche 2008; Killburn 2001; Koopman 2002; Woodcock 2004). Up until now the reasons behind the lack of effectiveness of these carefully designed studies remain unclear.

A possible explanation for the assumed superiority of multifaceted allergen reducing interventions over monofaceted counterparts is based on cross-reactivity of allergens of inhalant and food origin (Flinterman 2008). When a high-risk child is exposed to either one of the allergen types (inhalant or dietary), the risk of asthma might not be decreased. For this reason it seems likely that allergen-reducing interventions for asthma prevention should target both types of allergens (multifaceted intervention).

Based on theoretical considerations that asthma is a multi-factorial disease, successful prevention might only be demonstrated if most relevant environmental factors for a specific child are simultaneously avoided. To investigate this hypothesis we undertook a systematic review of mono- and multifaceted allergen avoidance interventions to prevent asthma in high-risk children, compared with controls. As we were aware that there are at present no randomised controlled trials directly comparing mono- and multifaceted interventions we considered that this approach would offer the possibility of an indirect comparison between these two intervention strategies.

OBJECTIVES

The objective of this review was to compare the effectiveness of mono- and multifaceted allergen reduction interventions in the primary prevention of asthma and asthma symptoms in children judged to be at high risk of developing asthma.

METHODS

Criteria for considering studies for this review

Types of studies

Birth cohort randomised controlled trials (RCTs) with follow up of children from birth onwards. The interventions tested were either multifaceted or monofaceted and focused on allergen exposure reduction (inhalant allergens and/or food allergens).

Types of participants

Children at high risk of developing atopy or asthma recruited at or before birth with the aim of preventing asthma. High risk of developing atopy or asthma was defined as a family history of atopy or asthma in at least one close relative (i.e. biologic parent or full sibling). We stipulated that the family history should be confirmed by parents, general practitioner (GP) or biological marker of hypersensitivity (specific IgE or skin prick test).

Types of interventions

Allergen reducing interventions focused on inhalant allergens and/or food allergens, either as part of a multifaceted or monofaceted intervention strategy. Co-interventions included in multifaceted or monofaceted interventions (not aimed at allergen reduction) were permitted.

We categorised studies as either multifaceted or monofaceted depending on whether they aimed at reducing exposure to inhalant allergens AS WELL AS food allergens (multifaceted) or whether they aimed at reducing exposure to EITHER inhalant allergens OR food allergens (monofaceted).

Control interventions needed to be in optimal contrast with the intervention group strategies. For this reason control group interventions included were either placebo strategies or usual care.

Allergen reduction measures started either during pregnancy or from birth onwards, and continued during postnatal life. The minimum duration of intervention was four months. We anticipated some variation in the length of follow up beyond this time point. Another Cochrane Review of pre and postnatal dietary intervention focused on maternal diet (Kramer 2006). However, in the current review we extend the focus to postnatal intervention in infants, and prenatal environmental allergen reducing interventions.

Types of outcome measures

Outcomes of interest needed to be assessed at a minimum age of two years. At least one clinical outcome measure (current asthma or respiratory symptoms, wheezing, nocturnal coughing and/or dyspnoea) had to be evaluated for studies to be eligible.

Asthma cannot be determined objectively in children under five years of age since lung function measurements cannot be performed reliably in these children. Nevertheless, we chose to include the outcome of current asthma in children < five years because doctors do diagnose children as being asthmatic at these young ages. The diagnosis of asthma in these young children is confirmed when the respiratory symptoms (wheezing, coughing

and dyspnoea) are successfully treated with asthma medication. We considered asthma diagnosed in children older than five years as a separate outcome.

Current nocturnal coughing is also included as an outcome although it is known that this is likely to be a manifestation of asthma in only a minority of cases, which makes it less reliable (Ninan 1995). However, as most studies in the field of asthma prevention use this criterion, we have included nocturnal coughing in the current meta-analyses.

Primary outcome

1. Current asthma, defined as doctor diagnosis in children aged < five years.
2. Current asthma, defined as current respiratory symptoms (wheeze and/or nocturnal coughing and/or dyspnoea) plus lung function criteria corresponding with a clinical diagnosis of asthma (bronchial hyper responsiveness (BHR) and/or reversibility) in children aged $\geq$ five years.

Secondary outcome

3. Current respiratory symptoms (wheeze, nocturnal coughing and dyspnoea) as reported by parents in questionnaires.
4. Adverse events.

Search methods for identification of studies

Eligible studies were identified by a computer aided search of the Cochrane Airways Group Trials Register in December 2008. There was no limitation on language of publication.

The following search terms were used:

- design related terms: clinical trial, random, intervention*, control*;
- illness related terms: asthma;
- topic related terms: prevent*, reduct*, allergen*.

In order to retrieve unpublished or unidentified studies we contacted experts in the field via a letter and a standardised e-mail.

Data collection and analysis

Selection of studies

Based on title and abstract one review author (TM) selected studies by applying the inclusion criteria to the studies identified by the literature search. In case of uncertainty, a second review author (CPvS) was consulted. Both review authors assessed the full paper version of the selected studies. Disagreements about inclusion were resolved by consensus.

Data extraction and management

Two review authors (TM and CPvS) extracted data from the included studies. Any discrepancies between the two authors were resolved by discussion. Data were extracted according to the following criteria.

- Methods: setting (location of intervention extramural, at home or hospital, country, year of study) and study design.
- Participants and/or healthcare providers: method of recruitment, inclusion criteria, characteristics of study population (gender, familial predisposition, number of older siblings).
- Interventions: description of the intervention for each group (mono- versus multifaceted interventions).
- Outcome measures: for each outcome measure (diagnosis of asthma and respiratory symptoms (wheezing, night-time cough and dyspnoea), the definition of outcome and specific outcome assessor).

Assessment of risk of bias in included studies

The authors were not blinded to article authors, institutions or journal titles. We assessed the methodological quality of the included studies on the items described in the 'Risk of bias' tables. The characteristics used for methodological evaluation were:

1. adequate sequence generation;
2. allocation concealed;
3. incomplete outcome addressed;
4. free of selective reporting;
5. blinding of 'patient'/parents;
6. blinding of healthcare provider;
7. blinding of outcome assessor;
8. balanced at baseline regarding the most important prognostic indicators (e.g. gender, familial predisposition of child, number of older siblings, pets);
9. inclusion and exclusion criteria specified;
10. specification of outcome measures.

Two review authors (TM and CPvS) independently assigned a score for criteria 1 to 10.

In a consensus meeting, disagreements between the two authors were discussed and resolved. If a study did not contain sufficient information on methodological criteria, we contacted the authors for additional information.

We included individual studies for meta-analysis if items numbered 1, 2, 6 and 10 at least had been described and fulfilled. The reason blinding of outcome assessors is found to be more important than blinding of the parents is that it seems unethical to keep parents uninformed on the treatment they help supply to their child. For outcome assessors, however, this problem does not occur and they might even be inclined to let interpretation of outcomes be influenced by the knowledge of the group subjects were allocated to.

Data synthesis

We used Review Manager 5 (RevMan 2008) for pooling data to assess the effects of specific interventions and report data on the same outcome measure. A formal test for statistical heterogeneity, the natural approximate Chi^2 test, assessed whether the observed variability in effect sizes was greater than would be expected to occur by chance. For dichotomous endpoints, we presented an odds ratio (OR) and 95% confidence interval (CI) using a random-effects model. We also re-analysed the data using a fixed-effect model and compared the two types of modelling. When only small differences were observed we presented the data using the random-effects model.

We calculated a number needed to treat (NNT) for the main outcome (asthma) at ages five years and older to define the number of children required to be treated in order for one to avoid the outcome of interest (Visual Rx). We did not calculate the NNT for diagnosis under five years as these diagnoses are less standardised. Due to the nature of the question addressed in this review, it was likely that there would be some variation in the length of follow up carried out in each of the studies. We therefore aimed to analyse data on diagnosis and symptoms of asthma in two ways. Firstly, we analysed data from multiple age categories (as age-pooled subgroups). For every outcome we also analysed data from the last published observation available in each of the studies, irrespective of time point. The results pooled as last observation available resulted in more data for pooling (n/N). A disadvantage of this type of pooling was the ages at which the outcome was evaluated tended to differ between the types of trials (mono- and multifaceted interventions).

We used intention-to-treat (ITT) analyses for all studies, even if they did not report these data. For all studies we assumed that cases lost to follow up did not satisfy the criteria for the outcome tested. To evaluate the plausibility of this assumption we performed sensitivity analyses for every outcome based on numbers of participants on-treatment (OT). If there were any major differences between the two types of analyses we reported the observations. The ITT results were the main outcome presented.

Subgroup analysis and investigation of heterogeneity

We made an indirect comparison of the effects of both types of interventions (multifaceted or monofaceted) by calculating the interaction with their confidence intervals (relative odds ratio), when data were available for both types of intervention studies. We used a test for interaction conforming to the method described by Altman & Bland 2003.

RESULTS

Description of studies

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

Results of the search

We screened a total of 1230 articles (including duplicates). After screening on title and abstract, 41 studies remained. We screened full paper versions of these 41 for inclusion, and broadened the search by checking relevant references.

Included studies

We included a total of nine studies. Some studies reported results at multiple time points. Of the included studies, three were classified as **multifaceted** intervention studies in the current meta-analyses: the Canadian study (Canadian study 2004; Canadian study 2005), the Isle of Wight study (Isle of Wight 1994; Isle of Wight 1997; Isle of Wight 2003) and PREVASC (PREVASC 2005). Six were classified as **monofaceted** intervention studies (CAPS HDM 2004; CAPS HDM 2006; Mallet 1992; nacMAAS 2004; PIAMA 2006; SPACE 2004; Zeiger 1989; Zeiger 1992; Zeiger 1995).

Multifaceted intervention studies

(Described with use of information from Maas 2005).

The *Canadian Childhood Asthma Primary Prevention Study* (Canadian study 2004; Canadian study 2005) included children at high risk of developing asthma or allergy during the prenatal period (267 control and 278 intervention families). The intervention tested was aimed at the reduction of **house dust mite** (impermeable bedding encasings and advice on washing, sanitation and ascaricidal treatment) and **pet allergen** exposure, **food allergen** exposure and reduction of exposure to **environmental tobacco smoke**. The food allergen reducing intervention started during prenatal life and was continued until the children reached the age of six months. Pregnant women were advised to follow a specific diet and mothers were encouraged to breastfeed their child completely for six months, supplemented with hypo-allergenic formula if necessary. They were asked to delay the introduction of their child to solid food followed by a stepwise standardised introduction of solids. Controls were not offered any intervention but followed standard usual care. Asthma outcome as last reported was measured at age seven by lung function measurement (bronchial hyper reactivity (BHR) < 7.8 mg/ml) combined with reported wheeze.

The *Isle of Wight study* (Isle of Wight 1994; Isle of Wight 1997; Isle of Wight 2003) included children at high risk of developing allergic diseases (dual heredity) during prenatal life (69 controls and 67 intervention families). The intervention tested was aimed at reduction of **house dust mite** (sanitation and ascaricidal treatment) and **pet allergen** exposure as well as exposure to **food allergens**. The food allergen reducing intervention started during postnatal life. Mothers were encouraged to breastfeed and during

the breastfeeding period they were advised to follow a strict dietary regimen and introduction to allergenic solids was advised to be delayed to nine months. Allergenic solid foods were introduced in stepwise fashion from then on. Controls were not offered any intervention but followed usual care. The asthma outcome as last reported was measured at age eight by lung function measurement (BHR < 8mg/ml) combined with reported asthma symptoms. The *PREVASC study* (Kuiper 2005; PREVASC 2005) included children during prenatal life. The allergen reducing intervention started from then on. **House dust mite allergen** reducing advice was provided (bedding encasings on parental and child bed, sanitation and washing advice), as well as advice on reduction of **pet allergens** (not inside) and **cigarette smoke** exposure (stop smoking). The **food allergen** reducing intervention consisted of encouragement to exclusively breastfeed until six months. If this was not feasible, supplementing with hypo-allergenic formula was advised. Solid foods were advised to be introduced from the age of six months on, with no standardised introduction to be followed. Controls were not offered any intervention and followed usual care. The diagnosis of current asthma as last reported was defined at age two. This diagnosis was reported to the research group by the participants' general practitioner in a standardised manner.

Monofaceted intervention studies

(Described with use of information from Maas 2005).

The *CAPS-study* (CAPS HDM 2004; CAPS HDM 2006) recruited participants during prenatal life in antenatal clinics (308 control and 308 intervention families). At least one parent or sibling did have to be a diagnosed asthmatic patient and had to have experienced current asthma symptoms. Families were excluded when there was a pet cat in the household and if they were on a strict vegetarian diet. The intervention used was focused on **house dust mite allergen** reducing measures. House dust mite allergen impermeable mattress encasings for the children and cleaning advice was provided. A latex-free play mat was provided by the research group to reduce contact of the children with carpeted floors. The control group families only received cleaning advice. No other research intervention was supplied. Asthma outcome as last reported was measured at age five by lung function measurement (FEV1) plus parental reported current wheeze and previous asthma diagnosis. If these criteria were not fulfilled a 12% increase of FEV1 after bronchodilator was defined as current asthma.

The study carried out by Mallet *et al* (Mallet 1992) recruited infants (hospital) during prenatal life, if atopic disease in first degree family members was confirmed by medical records. Eighty-five children were included in the control group and 92 were assigned to the intervention group. The intervention supplied was focused on **cow's milk allergen** reduction (casein hydrolysed formula) for four months either exclusively or as substitute to breastfeeding. No other food was allowed during these months. Control group families did receive normal cow's milk based formula. At age four years the outcome diagnosis asthma was identified at clinical as-

essment.

In the *naMAAS study* (naMAAS 2004) during prenatal life 146 infants were included in the control group and 145 were allocated to the intervention group, when both parents had atopic disease and no furry pets were present in the household. The intervention supplied was based on **house dust mite allergen** reduction by sanitation advice and house dust mite impermeable mattress encasings for the parental and child mattress from pregnancy on. House dust mite allergen reducing sanitation measures were supplied by the study. The control group families received usual care treatment. At age three years the asthma outcome was last reported and consisted of physician diagnosed asthma.

In the *PIAMA study* (Koopman 2002; PIAMA 2006) pregnant women were informed of the study and families were included if the mother reported to be allergic on the grounds of questionnaire data (395 families were allocated to the control group and 416 families formed the intervention group). The intervention supplied was focused on reduction of **house dust mite allergen** reduction by sanitation measures (advice) and allergen impermeable mattress covers. The control group intervention was based on supply of placebo mattress covers and sanitation advice (same as the intervention group received). At age four years the outcome was reported. No asthma diagnosis was described but asthma symptom outcome was reported (wheeze and night-time cough as reported by parents in questionnaires).

During pregnancy the *SPACE* (Halmerbauer 2003; SPACE 2004) study included 347 families in the control group and 349 were allocated to the intervention group. The intervention supplied was focused on **house dust mite allergen** reduction. Parents and infants were supplied with house dust mite impermeable mattress encasings. Both groups were informed about allergy and inhalant and food allergen reducing measures. The control group did not receive mattress encasings (no placebo intervention).

The *Zeiger study* (Zeiger 1989; Zeiger 1992; Zeiger 1995) tested the effectiveness of a **food allergen** reducing intervention. One-hundred and ninety-eight families were prenatally included in the control group and 153 families were allocated to the intervention group. The intervention started during the last trimester of pregnancy with advice on reduction of allergenic food as supplied by dieticians. If breastfeeding was supplemented or stopped, a casein based formula feed was provided to be used until 12 months of age. The control group families were encouraged to follow standard diets as provided by the Kaiser Permanente Obstetric Department. A cow's milk based whey formula was provided to the control group. At age seven the diagnosis of asthma, defined as physician documented lower respiratory disorder with reversible bronchospasm, was tested.

Excluded studies

Two studies (Johnstone 1966; Kjellman 1979) that did initially seem to fit the inclusion criteria were excluded because of insufficient methodological quality (outcome assessors not blinded and

allocation concealment not clear).

The study of Kjellman did test the effectiveness of a **food allergen** reducing intervention (use of soy formula).

Johnstone et al did also test the preventive effectiveness of a **food allergen** reducing intervention (use of soy formula).

The study of Chandra 1997 (**cow's milk allergen**) initially did fit the inclusion criteria but was excluded because of evidence that the published data may have been fabricated (Kramer 2006).

One study (Koopman 2002) did fit the inclusion criteria but no information was supplied on the prevalence of outcomes; the only results described in the paper were those of a multiple regression analysis. From this study only outcome at age four (PIAMA-study, **house dust mite allergen**) was included in the current meta-analysis.

Twenty-two studies were excluded for various reasons as described in the table 'Characteristics of excluded studies' (Arshad 1992; Boggs 2003; Bottcher 2002; Brunekreef 2002; CMA 2005; Chandra 1997; Chan-Yeung 2002; Custovic 2000a; Custovic 2000b; Custovic 2001; Dunstan 2003; Kalliomaki 2001; Kjellman 1979; Koopman 2002; Mihrshahi 2001; Marks 2006; Marini 1996; Peat 2004; Saarinen 1979; Simpson 2003; Simpson 2004; van Strien 2002).

Risk of bias in included studies

The methodological quality of included studies is presented in the 'Risk of bias' tables. The items that were crucial for inclusion were randomisation performed, allocation concealed, outcome assessor blinded and specifications of outcome measures. When one or more of these items was not described the study was excluded. The authors' assessment of the risks of bias are summarised in Figure 1 and Figure 2.

Figure 1. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.

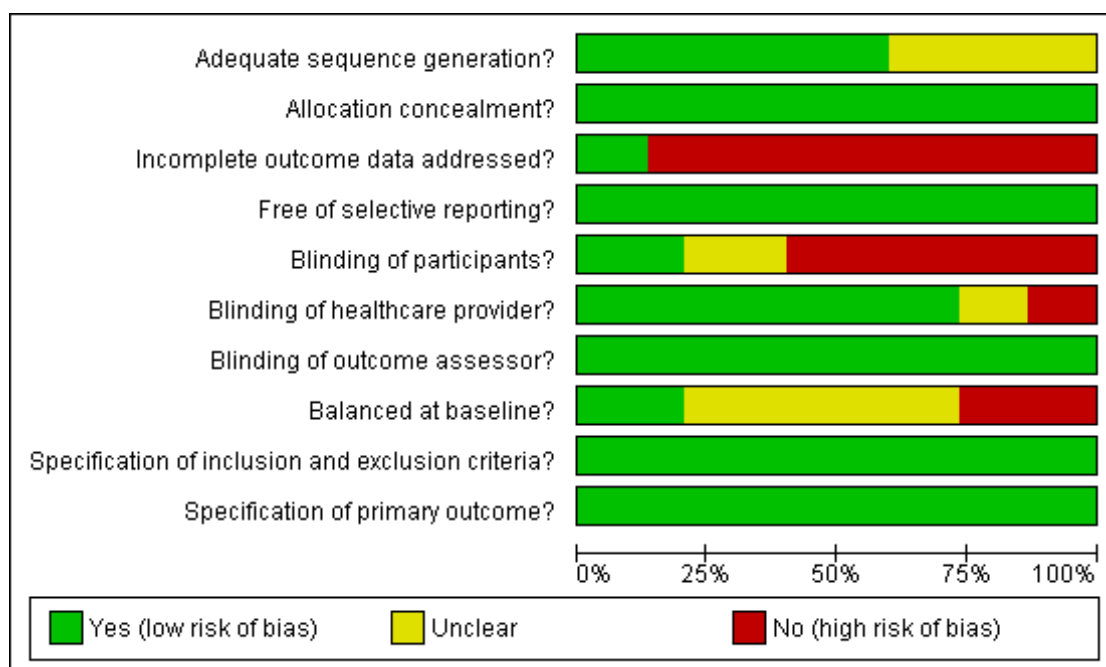


Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

	Adequate sequence generation?	Allocation concealment?	Incomplete outcome data addressed?	Free of selective reporting?	Blinding of participants?	Blinding of healthcare provider?	Blinding of outcome assessor?	Balanced at baseline?	Specification of inclusion and exclusion criteria?	Specification of primary outcome?
Canadian study 2004	+	+	-	+	-	+	+	?	+	+
Canadian study 2005	+	+	-	+	-	+	+	?	+	+
CAPS HDM 2004	+	+	-	+	-	?	+	+	+	+
CAPS HDM 2006	+	+	-	+	-	?	+	+	+	+
Isle of Wight 1994	?	+	-	+	-	+	+	-	+	+
Isle of Wight 1997	?	+	-	+	-	+	+	-	+	+
Isle of Wight 2003	?	+	-	+	-	+	+	-	+	+
Mallet 1992	?	+	-	+	+	-	+	?	+	+
nacMAAS 2004	?	+	-	+	-	+	+	?	+	+
PIAMA 2006	?	+	+	+	+	+	+	-	+	+
PREVASC 2005	+	+	+	+	-	-	+	+	+	+
SPACE 2004	+	+	-	+	+	+	+	?	+	+
Zeiger 1989	+	+	-	+	?	+	+	?	+	+
Zeiger 1992	+	+	-	+	?	+	+	?	+	+
Zeiger 1995	+	+	-	+	?	+	+	?	+	+

Effects of interventions

We included three multifaceted allergen reducing intervention trials, some with an additional co-intervention (for example, environmental tobacco smoke (ETS) reduction) on prevention of asthma in children at high risk of developing asthma ($n = 1157$). We also included six monofaceted allergen-reducing trials ($n = 2131$), again some of which had an additional intervention like dietary fatty acid modification. Data from these studies were pooled separately at several age-specific time points under the outcomes:

- 'current asthma (defined as doctor diagnosis) in children aged < five years';
- 'current asthma (defined as current respiratory symptoms (wheezing and/or nocturnal coughing and/or dyspnoea) plus lung function criteria corresponding with clinical diagnosis asthma (BHR and/or reversibility) in children aged $\geq$ five years'; and
- 'current respiratory symptoms' (wheezing, nocturnal coughing, dyspnoea) as recorded by parents/carers in questionnaires.

Adverse events were not described in any of the included studies.

Current asthma (defined as doctor diagnosis) in children aged < five years

Multifaceted intervention studies favoured treatment at two years of age; the pooled results of [Canadian study 2004](#), [Isle of Wight 1994](#) and [PREVASC 2005](#) showed an odds ratio (OR) of 0.71 (95% CI 0.53 to 0.95). At four years of age one study ([Isle of Wight 1997](#)) was included and showed an OR of 0.56 (95% CI 0.26 to 1.23). The overall outcome 'current asthma in children aged < five years last reported' resulted in an OR of 0.72 (95% CI 0.54 to 0.96) (see [Figure 3](#)).

monofaceted intervention studies did not show a significant difference compared with control when data from children at two years of age from [CAPS HDM 2004](#), [Mallet 1992](#); [nacMAAS 2004](#); [SPACE 2004](#) and [Zeiger 1989](#) were combined (OR 0.88, 95% CI 0.48 to 1.64). The results of the pooling of data from the studies of [CAPS HDM 2004](#) and [nacMAAS 2004](#) at age three years resulted in an OR of 0.84 (95% CI 0.41 to 1.71). At four years of age the results of [Mallet 1992](#) and [Zeiger 1992](#) were pooled (OR 1.09, 95% CI 0.60 to 1.98). Data in children aged between two and five years analysed at last available assessment did not identify a significant difference in the likelihood of physician-diagnosed asthma between treatments (OR 1.12, 95% CI 0.76 to 1.64) (see [Figure 4](#)).

Figure 3. Forest plot of comparison: I Current diagnosis asthma ITT, outcome: I.1 Multifaceted intervention.

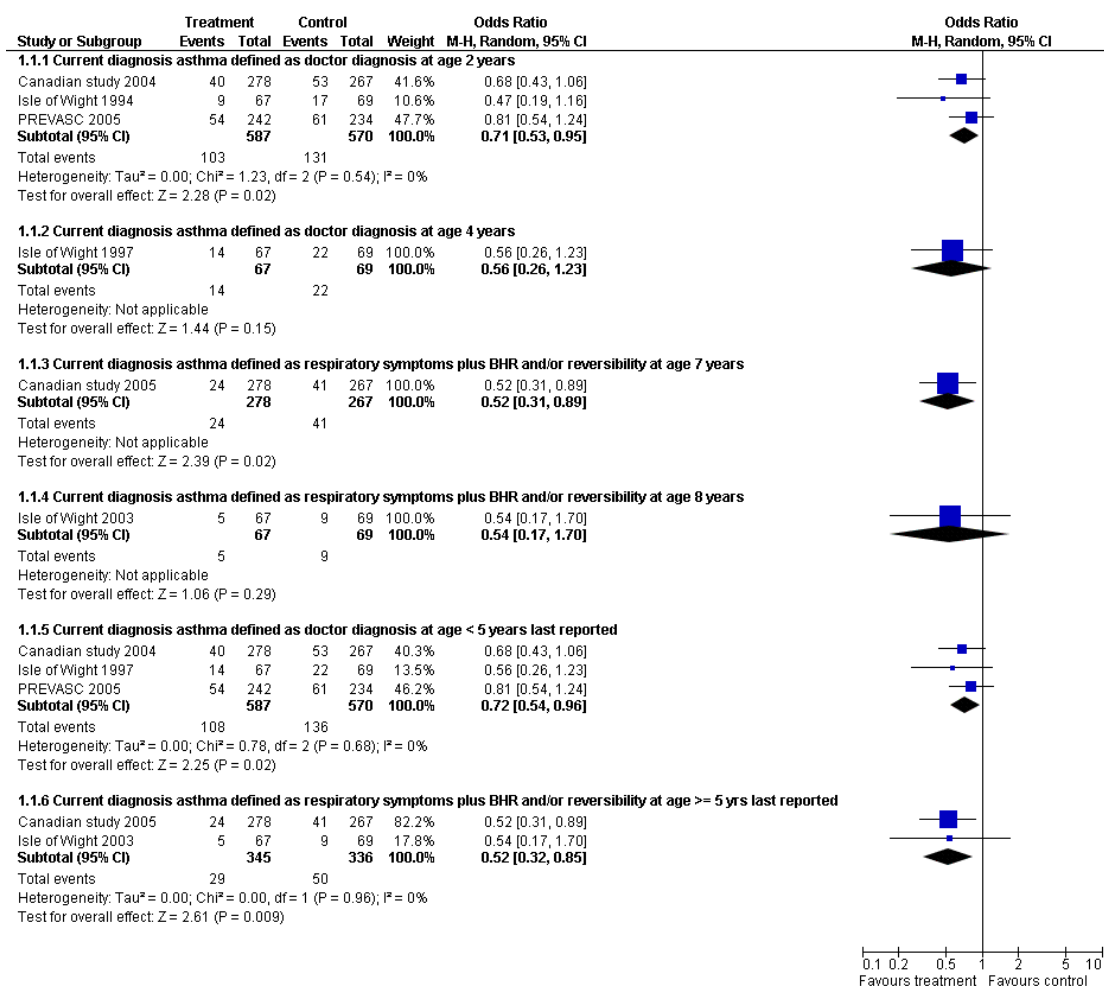
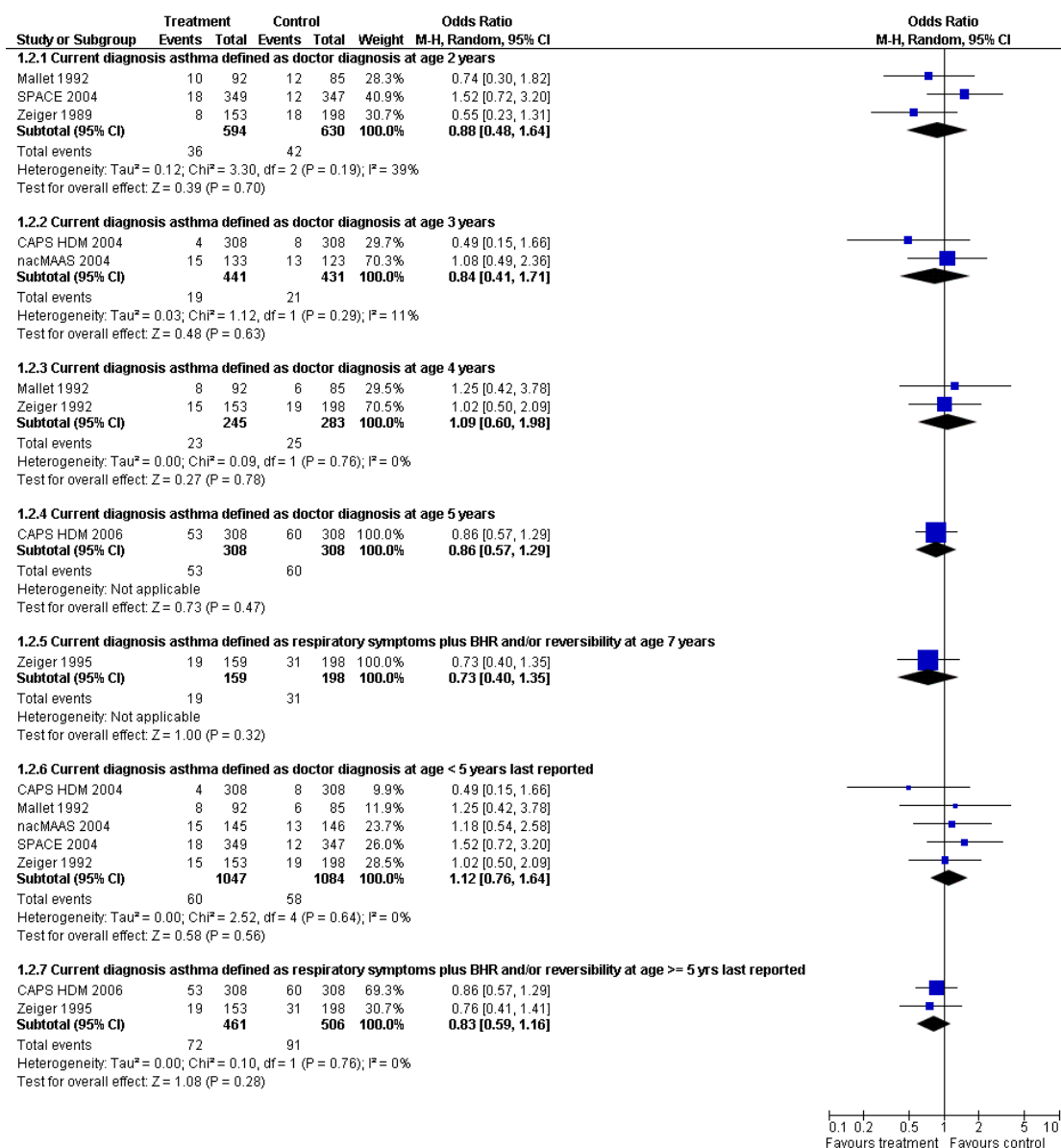


Figure 4. Forest plot of comparison: I Current diagnosis asthma ITT, outcome: 1.2 monofaceted intervention.



The test for interaction (Altman & Bland 2003) between multifaceted and monofaceted results for the outcome 'current asthma (defined as doctor diagnosis) in children aged < five years' showed a relative OR of 0.64 (95% CI 0.40 to 1.04, $P = 0.07$), which indicated that there was not a significant difference between the two types of interventions.

Current asthma (defined as presence of current respiratory symptoms (wheeze and/or nocturnal coughing and/or dyspnoea) PLUS lung function criteria corresponding with a clinical diagnosis of asthma (BHR and/or reversibility), in children aged > five years

Multifaceted intervention studies described results at ages seven and eight years using the definition of diagnosis of asthma 'presence of current wheezing plus BHR'. The studies showed a pooled OR for a diagnosis of asthma of 0.52 (95% CI 0.32 to 0.85). Two monofaceted intervention studies reported asthma symptoms at five years and older. CAPS HDM 2006 reported data on current respiratory symptoms and reversibility OR asthma diagnosis by a healthcare professional at five years. Zeiger 1995 reported data on diagnosis of asthma defined as current respiratory symptoms and reversibility at age seven years. Current asthma in children aged > five years at last assessment was not significantly different between treatment and control (OR 0.83, 95% CI 0.59 to 1.16).

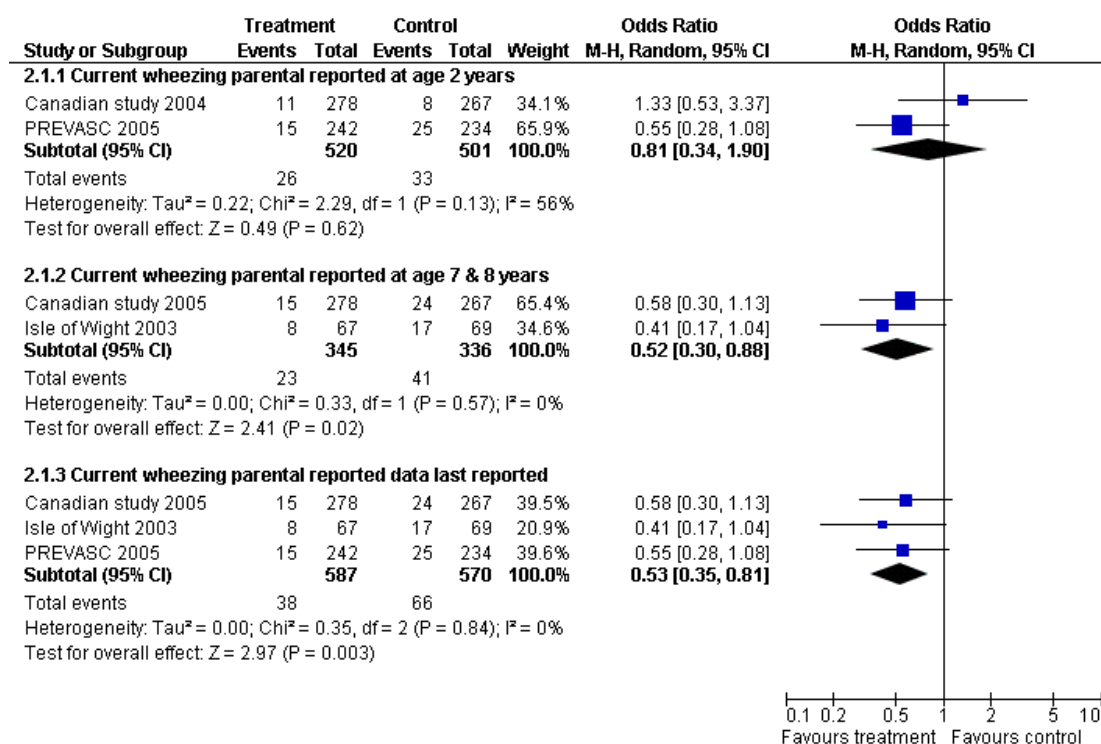
The interaction between multifaceted and monofaceted results for the outcome 'current asthma (defined as presence of respiratory symptoms plus lung function criteria corresponding with a clinical diagnosis of asthma' was a relative OR of 0.63 (95% CI 0.35 to 1.13, $P = 0.12$), which indicates that there is no significant difference between the two types of interventions. The times of last assessment were at slightly younger ages in monofaceted trials (five and seven years) as compared to those with a multifaceted approach (seven and eight years) but as these ages are not dramatically different this is not expected to have influenced the outcome of the comparison.

Current respiratory symptoms

Wheezing

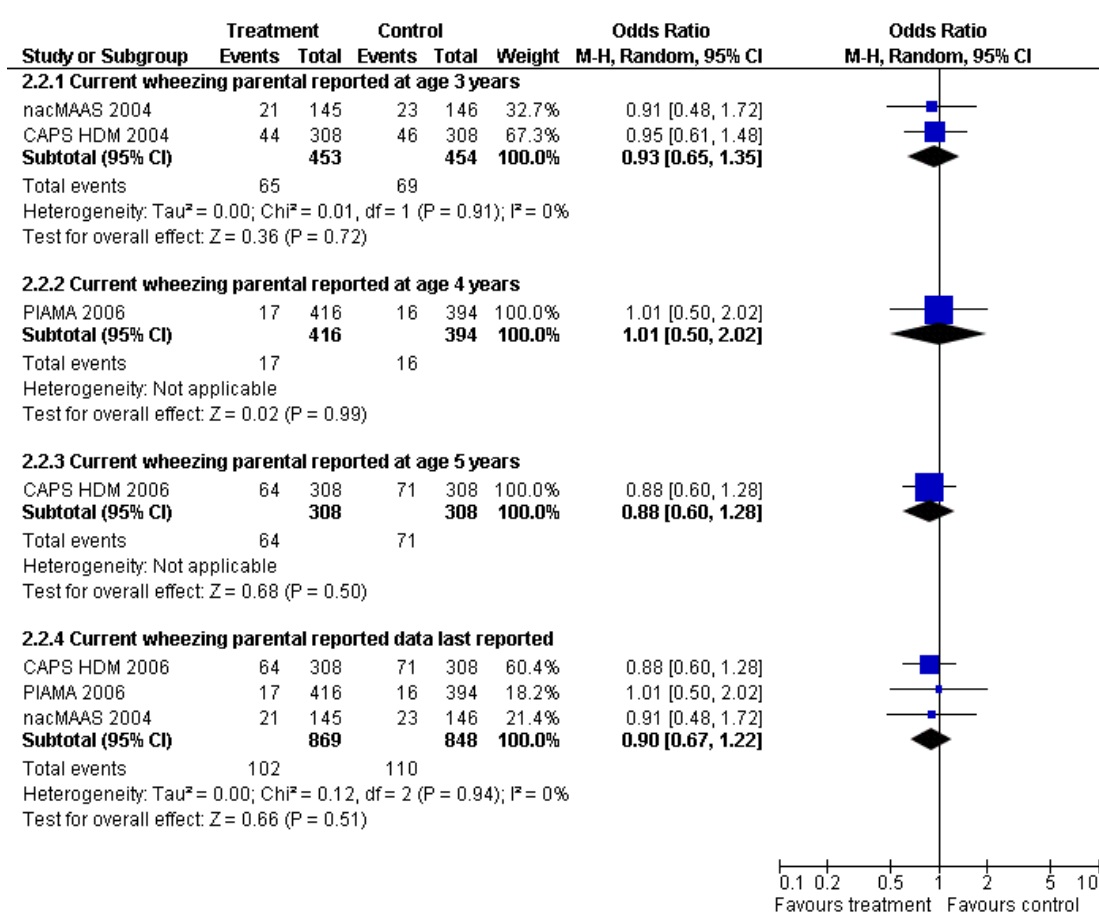
As described for multifaceted interventions, wheezing was reported at the ages two, seven and eight years and only at age two years could data be pooled age-specifically. The results of this pooling of data at two years were not significantly different between treatment and control (Canadian study 2004; PREVASC 2005: OR 0.81, 95% CI 0.34 to 1.90). When pooled at age seven and eight years the result was OR 0.52 (95% 0.30 to 0.88). Wheeze at last reported assessment was in favour of treatment (Canadian study 2005; Isle of Wight 2003; PREVASC 2005: OR 0.53, 95% CI 0.35 to 0.81) (see Figure 5).

Figure 5. Forest plot of comparison: 2 Current wheezing parental reported ITT, outcome: 2.1 Multifaceted.



Outcome of monofaceted intervention studies was described for children at aged three, four and five years. Two studies reported data for the outcome of wheezing at three years of age (CAPS HDM 2004; nacMAAS 2004) and pooling resulted in an OR of 0.93 (95% CI 0.65 to 1.35). Pooling of data for 'current wheezing as last reported' was shown to be non-significant (CAPS HDM 2006; nacMAAS 2004; PIAMA 2006: OR 0.90, 95% CI 0.67 to 1.22) (see Figure 6).

Figure 6. Forest plot of comparison: 2 Current wheezing parental reported ITT, outcome: 2.2 monofaceted.

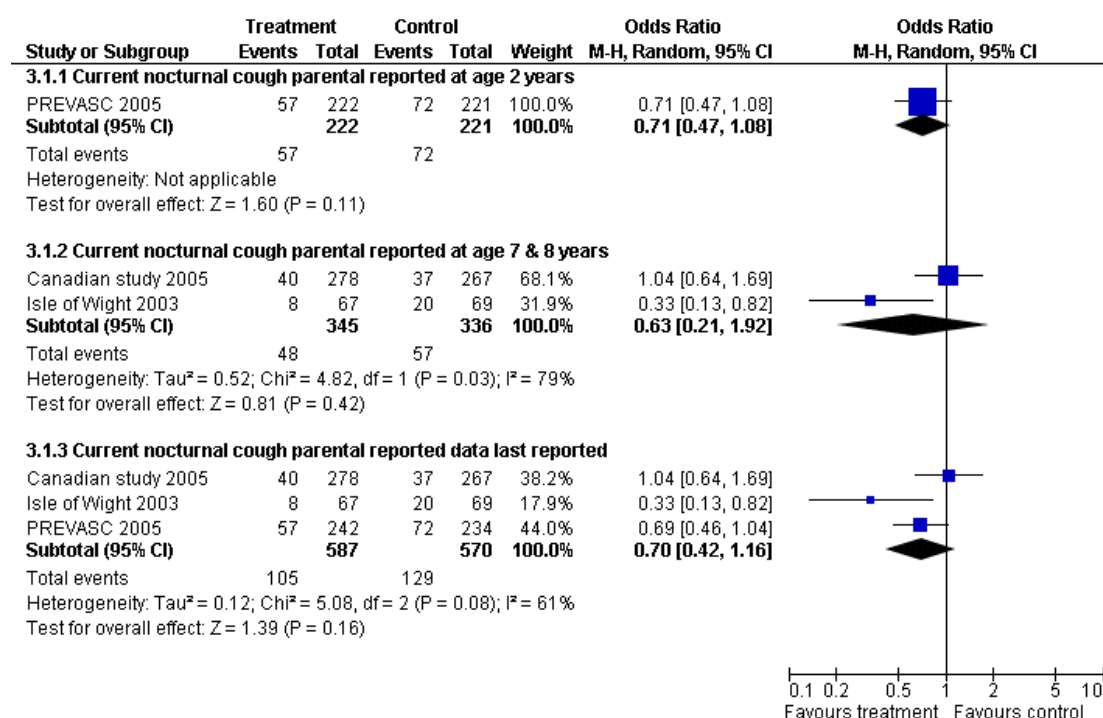


The interaction between multifaceted and monofaceted results for the outcome 'current wheezing' was a relative OR of 0.59 (95% CI 0.35 to 0.99, $P = 0.04$), which indicates a significant difference between the two types of interventions in favour of multifaceted interventions. It should be noted that the age of last assessment was later for the multifaceted intervention (two to eight years) than for the monofaceted intervention (three to five years). It is plausible that the difference in timing of outcome measurement has influenced the result of the comparison of intervention types.

Nocturnal coughing

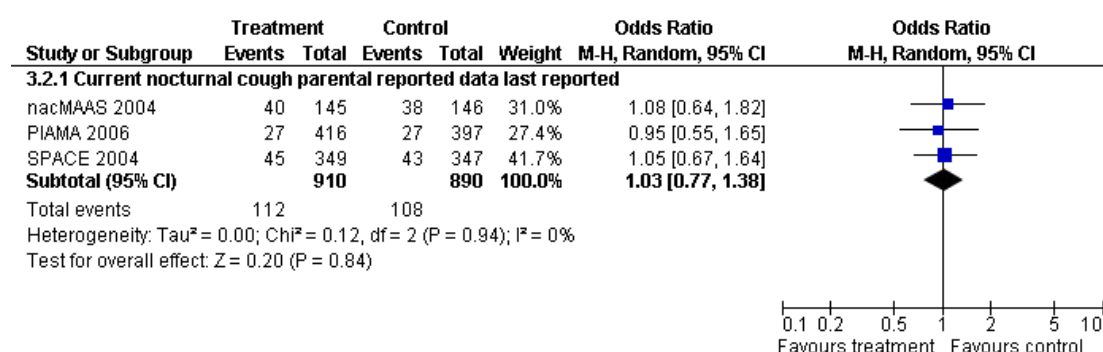
This was reported for multifaceted intervention studies at ages two, seven and eight years (Canadian study 2005; Isle of Wight 2003; PREVASC 2005) and again could not be age-specifically pooled. Only the outcome 'current nocturnal coughing as last reported' could be pooled. This pooling of last reported data showed an OR of 0.70 (95% CI 0.42 to 1.16) (see Figure 7).

Figure 7. Forest plot of comparison: 3 Current nocturnal cough parental reported ITT, outcome: 3.1 Multifaceted.



Three monofaceted randomised controlled trials described the outcome 'current nocturnal coughing as reported by parents in questionnaires' (nacMAAS 2004; PIAMA 2006; SPACE 2004). Pooling of data from these studies at two, three and four years resulted in an OR of 1.03 (95% CI 0.77 to 1.38) (see Figure 8).

Figure 8. Forest plot of comparison: 3 Current nocturnal cough parental reported ITT, outcome: 3.2 monofaceted.



The interaction between multi- and monofaceted results for the outcome of current nocturnal coughing was a relative OR of 0.68 (95% CI 0.38 to 1.22, $P = 0.20$), again a non-significant difference between intervention types. Again the ages of last assessment were later in the multifaceted intervention studies (two to eight years) as compared to the monofaceted studies (two to four years). This difference in outcome measurement could have influenced the result of the comparison of interventions.

The only study that reported **current dyspnoea** as an outcome was the multifaceted intervention study PREVASC (PREVASC 2005). The age at which this outcome was reported was two years. The OR found in the PREVASC study was 1.18 (95% CI 0.67 to 2.08).

Sensitivity analyses

To evaluate the plausibility of the assumption we made that those cases lost to follow up did not meet the criteria of the outcome tested, we analysed the results of cases on-treatment (OT). The statistical significance of the relative OR favouring multi over monofaceted interventions disappeared when our sensitivity analysis was applied to data on current wheezing (relative OR 0.64, 95% CI 0.38 to 1.06).

We carried out sensitivity analyses (analyses not included in this paper) in which we sought to determine whether removing studies of postnatal intervention gave similar results to our primary analyses of all studies. The results of these analyses were compared between multi- and monofaceted studies. These analyses revealed that the time of the start of the intervention did not alter the direction of the results.

Stratification for duration of intervention did not result in any useful information for the research question we postulated, as comparisons of mono- and multifaceted studies were rarely possible

due to large variations in duration of the intervention.

Sensitivity analyses on the difference between type of mono-intervention were carried out, with separate pooling of single house dust mite interventions and single food allergen reducing interventions. The results of these analyses did not provide any differing information. These analyses are not presented in this review.

DISCUSSION

To evaluate our hypothesis that multifaceted interventions are superior to a monofaceted approach, we carried out meta-analyses of monofaceted and multifaceted allergen reducing intervention studies. We performed tests for interaction on the indirect comparisons of these pooled estimates at last assessment for all outcomes where available.

monofaceted intervention versus control

The effects of monofaceted intervention compared with control did not indicate a significant reduction in diagnosed asthma, or in any of the symptom-related endpoints we assessed.

Multifaceted intervention versus control

Several of the tested outcomes tended to favour treatment with a multifaceted intervention when pooled at specific age time points, and when combining relevant time points (outcomes as last reported) over control. Based on the event rates in the control groups

of the two studies reporting data at more than five years, 17 children would need to be treated with this form of intervention to prevent one child receiving a diagnosis of asthma after five years ([Visual Rx](#)).

Two of the multifaceted allergen reducing intervention studies ([Canadian study 2004](#); [PREVASC 2005](#)) also used an intervention for tobacco smoke exposure reduction. Reducing tobacco smoke exposure has been associated with a reduction in asthma symptoms ([Stuart 2004](#)). Considering the low percentage of parents smoking in these study groups, it seems unlikely that this has distorted the results of the analyses carried out. It is feasible that the presence of an additional environmental intervention such as this may confound the treatment effect, particularly in families where exposure to tobacco smoke is high. Future studies which are concerned primarily with exposure to allergens and not toxicants should make provision for such an intervention in the control group so as to ensure that the independent variable is reduced exposure to allergens alone.

Indirect comparison of results

From the evaluation of the tests for interaction, multiple intervention strategies were more successful than single intervention strategies when current wheezing was assessed, although this outcome was assessed in an older age group in the multifaceted treatments. When data for children on-treatment were evaluated, however, no significance was reached.

The test of interaction was carried out for the outcomes of diagnosis of asthma as last reported at ages $\geq$ five years and under five years of age, and neither showed statistical significance in favour of multifaceted interventions. Comparison of wheezing and nocturnal coughing associated with asthma did not reach significance when comparing the two approaches.

The results of the current meta-analyses indicate that the development of asthma may be prevented to a greater extent by reducing several exposures at the same time, but this observation is from an indirect comparison and was only significant for the outcome of current wheezing. The results of these meta-analyses should therefore be interpreted with caution as the method of testing the hypothesis, by separate pooling of data of mono- and multifaceted randomised controlled trials, is not a direct randomised comparison. These separate trials all have differences in design and outcome definitions, and concomitant differences in types of outcome measurements and ages at which outcome measurement was carried out.

Results of sensitivity analyses on starting point and duration of intervention did not alter the direction of the effect of multi- or monofaceted interventions.

A possible confounding factor in the indirect comparison of results of mono- and multifaceted studies for the outcome of asthma at age < five years seems to be the differences in outcome definition. In some studies the outcome of asthma was defined during usual

care visits whereas other studies chose to evaluate this outcome during standardised physical examinations by a doctor associated with the research project.

Another possible confounding factor in the indirect comparisons we carried out might have been the variation in definition of the control intervention (placebo or usual care). As all multifaceted intervention studies used usual care as control intervention and monofaceted studies often used placebo interventions, we could not test the possible occurrence of this confounding factor by carrying out a sensitivity analysis.

Summary

The hypothesis that asthma may be better prevented by reduction of exposure to multiple allergens simultaneously might be correct, at least for current wheezing. The non-significant outcome for the comparison of mono- and multifaceted interventions at age five years and older might have been related to confounding factors caused by the indirect comparison of study results of both types of intervention. Specific differences that might have confounded the outcome might have been the difference in definition of control intervention, lack of power and difference in study outcome used in the types of studies compared, but the results might have been a true rendering of negative outcome. Multifaceted intervention studies, for example, reported data on diagnosis of asthma defined as respiratory symptoms and bronchial hyper responsiveness (BHR), and monofaceted intervention studies reported data on current diagnosis of asthma defined as respiratory symptoms plus reversibility as measured by a healthcare professional or the study investigators. Also, the definitions of control interventions were not similar between intervention types.

The possible difference between multiple interventions and monofaceted intervention might be sufficient to justify studies which compare differing intensities of exposure reduction. An efficient way testing the hypothesis we have drawn from the indirect comparison formulated, would be by designing a study in which both types of interventions are performed and directly compared in the same study. To our knowledge studies designed like this have never been performed to date. Factors complicating the performance of such a study are the large number of participants needed to secure the power of the study, the minimum follow up duration of six years to secure the success rate of lung function measurements and the concomitant costs. Such a study, however, will be of great importance for shedding new light on the prevention of the development of asthma in genetically susceptible children, and the current meta-analyses might inspire researchers to undertake this research.

AUTHORS' CONCLUSIONS

Implications for practice

The current meta-analyses suggest that multifaceted interventions, characterised by dietary allergen reduction and environmental remediation, might reduce the odds of a physician diagnosis of asthma later in childhood, in children who are at risk of developing childhood asthma, by a half. This translates to a number needed to treat (NNT) of 17. However, the effect of multifaceted interventions on parent reported wheeze was inconsistent and had no significant effect on nocturnal coughing or dyspnoea. monofaceted interventions were not significantly different from controls in the reduction of all outcomes.

Implications for research

The evidence base for the benefit of multifaceted interventions is limited to three studies that compared this to usual care, and further work is needed to establish both the effectiveness and cost-effectiveness of these interventions, preferably in comparison to placebo interventions (such as dummy mattress covers). There is also a need for direct head-to-head comparative trials of mono- and multifaceted allergen reduction strategies. These should be administered from birth and involve at least six years of follow up. It will be of crucial importance that researchers follow the guidelines for diagnosing asthma for the study outcome, and that the diagnosing physician remains blinded to group allocation. The cost-effectiveness of the intervention strategy and its possible effect on family dynamics and mental health status should be formally evaluated.

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Visual Rx

Cates CJ. Visual Rx 2.0. www.nntonline.net 2003.

Woodcock 2004

Woodcock A, Lowe LA, Murray CS, Simpson BM, Pipis SD. Early life environmental control: effect on symptoms, sensitization, and lung function at age 3 years. *American Journal of Critical Care Medicine* 2004;**170**(4):433–9.

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Canadian study 2004

Methods	Longitudinal birth cohort study with follow up of children from prenatal period to 7 years of age Providers and outcome assessors were blinded Number of drop-outs at 2 years of age: 69, of which n = 33 in the intervention group and n = 36 in the control group
Participants	Recruitment n=278 in the intervention group and 267 controls in 2 prenatal clinics Inclusion criteria: - pregnant women included during third trimester of pregnancy; - minimally one first degree family member of child is diagnosed with asthma or 2 first degree relatives of child diagnosed with other classic IgE mediated allergic diseases, both as measured by short questionnaire. Exclusion criteria: - intention to move away from city of recruitment within 2 years; - number of participants: 545.
Interventions	Multifaceted intervention: - reducing exposure to HDM by using impermeable bedding encasings and advice on washing and sanitation as well as use of acaricide treatment of furniture; - advice on reducing exposure to pet allergens; - advice on reducing exposure to ETS; - feeding advice for mothers during 3rd trimester of pregnancy and lactation period; - encouragement of breastfeeding completely for 6 months with formula (hypo-allergenic) supplementation if necessary; - delay of introduction of solid foods until 6 months and stepwise standardised introduction of solids. Control group intervention: usual care
Outcomes	Clinical outcome measures: - probable asthma, defined as at least 2 distinct episodes of cough or 2 episodes of wheeze and at least one of the following: nocturnal cough at least once a week (in the absence of cold), hyperpnea-induced cough or wheeze, response to treatment with beta agonists, anti-inflammatory drugs or both; - possible asthma, defined as 2 distinct episodes of wheeze, each lasting 1 or more weeks, or, in the absence of a cold, at least one of the following: nocturnal cough, hyperpnea-induced cough, or wheeze; - recurrent wheeze at age 1 and 2 years; - recurrent cough; - atopy, defined as a positive skin prick test reaction to 1 or more common inhalant or ingestant allergens.

Canadian study 2004 (Continued)

Notes	Asthma outcome as included in current meta-analysis is symptom diagnosis asthma (sum of possible and probable asthma) as diagnosed by paediatrician associated with study Outcome recurrent wheeze as reported in article fits inclusion criteria for outcome current wheezing in current meta-analysis	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Adequate sequence generation?	Yes	A adequate
Allocation concealment?	Yes	A adequate
Incomplete outcome data addressed? All outcomes	No	C inadequate
Free of selective reporting?	Yes	A adequate
Blinding of participants?	No	C inadequate
Blinding of healthcare provider?	Yes	A adequate
Blinding of outcome assessor?	Yes	A adequate
Balanced at baseline?	Unclear	B unclear
Specification of inclusion and exclusion criteria?	Yes	A adequate
Specification of primary outcome?	Yes	A adequate

Canadian study 2005

Methods	See above Number of drop-outs at 7 years of age for all outcome variables: 80, of which in intervention group and control group (n = 40 and n = 40)
Participants	See above
Interventions	See above

Canadian study 2005 (Continued)

Outcomes	Clinical outcome measures: - asthma, as diagnosed by paediatric allergist associated with study (structured interview and questionnaire as well as physical findings); - diagnosis asthma, defined as wheeze plus BHR; - defined as BHR (PC20 $\leq$ 7.8); - asthma symptoms: wheeze (apart from colds), nocturnal awakening caused by wheeze, night-time cough apart from colds; - diagnosis atopic eczema (paediatric allergist diagnosis); - allergic rhinitis; - nasal symptoms apart from colds; - skin rash lasting for > 6 months; - atopy defined as positive skin test to > 1 allergen.
Notes	Outcome current wheezing as included in current meta-analysis is described in article as wheeze apart from colds Outcome nocturnal cough as included in current meta-analysis is reported in article as cough at night apart from colds

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	A adequate
Allocation concealment?	Yes	A adequate
Incomplete outcome data addressed? All outcomes	No	C inadequate
Free of selective reporting?	Yes	A adequate
Blinding of participants?	No	C inadequate
Blinding of healthcare provider?	Yes	A adequate
Blinding of outcome assessor?	Yes	A adequate
Balanced at baseline?	Unclear	B unclear
Specification of inclusion and exclusion criteria?	Yes	A adequate
Specification of primary outcome?	Yes	A adequate

CAPS HDM 2004

Methods	Longitudinal birth cohort intervention study with follow up of children from pregnancy to 5 years Patients and providers were blinded, outcome assessors not clear if blinded or naive Number of drop-outs at age 3 years: n = 62 evenly divided over groups 31/31)
Participants	Recruitment n = 308 in intervention group and 308 controls in 6 antenatal clinics and private obstetric rooms in the study region Parents were asked to fill in questionnaires on asthma symptoms in the family Inclusion criteria: - at least 1 parent or sibling with current asthma symptoms; - living in study area; - reasonable fluency in English; - telephone at home. Exclusion criteria: - pet cat in the house; - strict vegetarian diet; - birth < 36 weeks gestation; - multiple birth; - birth weight < 2.5 kg; - significant neonatal disease, impairment or malformation; - hospitalisation > 1 week; - babies in need of surgery. Number of participants: 616 of which n = 308 in the HDM intervention group and n = 308 in the HDM control group
Interventions	HDM reducing intervention: monofaceted intervention on reduction of HDM allergen exposure - use of impermeable mattress encasing for child; - advice on reducing furry pets in child's bed and avoiding sheepskin underlays in child's bed; - latex-free play mat was provided to reduce contact with carpeted floors; - washing advice for bedding and play mat (acaricide washing); - cleaning advice. Control group intervention: only cleaning advice
Outcomes	Clinical outcomes (clinical examination and questionnaire): - no asthma; - trivial asthma, defined as wheeze in last 18 months; - infrequent episodic asthma, defined as 1 or more episodes of wheeze with attacks more than 6 weeks apart; - frequent episodic asthma, defined as 3 or more episodes of wheeze with attacks less than 6 weeks apart; - persistent asthma defined as 3 or more episodes of wheeze and at least 1 episode of night-time cough lasting more than 3 nights and wheeze attacks less than 6 weeks apart and daily use of asthma medication; - no cough;

	- mild cough, defined as cough for more than 1 week or cough without cold or nocturnal cough or cough during exercise and physical activity; - moderate cough, defined as presence of all 4 types of cough; - no wheeze; - non-atopic wheeze; - atopic wheeze; - no eczema; - non-atopic eczema; - atopic eczema; - atopy to ingested allergens; - atopy to inhalant allergens; - house dust mite atopy.	
Notes	Outcome asthma as included in current meta-analysis is reported in article as persistent asthma. We concluded this outcome did fit the inclusion criterion 'Current asthma (defined as doctor diagnosis) in children aged < five years since this outcome was the result of clinical examination (doctor?) Outcome trivial asthma (wheeze in last 18 months) as reported in article fits inclusion criteria outcome 'current wheeze' (wheeze in last 12 months) as included in current meta-analysis	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Adequate sequence generation?	Yes	A adequate
Allocation concealment?	Yes	A adequate
Incomplete outcome data addressed? All outcomes	No	C inadequate
Free of selective reporting?	Yes	A adequate
Blinding of participants?	No	C inadequate
Blinding of healthcare provider?	Unclear	B unclear
Blinding of outcome assessor?	Yes	A adequate
Balanced at baseline?	Yes	A adequate

CAPS HDM 2004 (Continued)

Specification of inclusion and exclusion criteria?	Yes	A adequate
Specification of primary outcome?	Yes	A adequate

CAPS HDM 2006

Methods	See above Number of drop-outs period 3 to 5 years n = 15, evenly divided over groups (8/7)
Participants	See above
Interventions	See above
Outcomes	Clinical outcomes: - probable current asthma, defined as parental report of any wheeze in last 12 months and either a parental report of any wheeze in last 12 months and previous parental report of diagnosed asthma (18 months, 3 years, 5 years) or 12% increase of FEV1 after bronchodilator at age 5 years; - frequent episodic wheeze, defined as 3 or more episodes and more than every 6 weeks over a period of 12 months; - infrequent episodic wheeze, defined as fewer wheezing episodes than frequent episodic wheeze; - other wheeze; - no wheeze; - persistent wheeze, defined as wheeze present at age 18 months and/or 3 years and also present at age 5 years; - late onset wheeze, defined as wheeze absent at 18 months and 3 years but present at age 5 years; - transient early wheeze, defined as wheeze present at age 18 months and 3 years but absent at age 5 years; - never wheezed; - cough without cold, defined as parental reported cough lasting $\geq$ 1 week not associated with cold; - rhinitis; - current eczema; - SPT: any atopy, inhalant atopy, HDM atopy, IgE IU/l; - baseline spirometry: FEV1 l, FEV1/FVC ratio; - post-bronchodilator spirometry: FEV1 l, FEV1/FVC ratio, % change FEV1; - FOT baseline: Rrs (cm H2O/l/s); - FOT after bronchodilator: Rrs (cm H2O/l/s), % change Rrs
Notes	Outcome persistent wheeze did fit the inclusion criteria of current wheeze (wheeze at 5 years of age, questionnaire data) although the symptoms in this study were the result of an interview including questions using a pro forma questionnaire

<i>Risk of bias</i>		
Item	Authors' judgement	Description
Adequate sequence generation?	Yes	A adequate
Allocation concealment?	Yes	A adequate
Incomplete outcome data addressed? All outcomes	No	C inadequate
Free of selective reporting?	Yes	A adequate
Blinding of participants?	No	C inadequate
Blinding of healthcare provider?	Unclear	B unclear
Blinding of outcome assessor?	Yes	A adequate
Balanced at baseline?	Yes	A adequate
Specification of inclusion and exclusion criteria?	Yes	A adequate
Specification of primary outcome?	Yes	A adequate

Isle of Wight 1994

Methods	Longitudinal birth cohort study with follow up of children from pregnancy to 8 years Providers and outcome assessors were blinded Number of drop-outs at age 2 years: n = 16, of which n = 11 in the intervention group and n = 5 in the control group No participants lost to follow up after the children had reached the age of 2 years
Participants	Recruitment of n = 67 in the intervention group and 69 controls at one district hospital at 28 weeks gestation Inclusion criteria: - pregnant women maximum gestational age child 32 weeks; - reported dual allergic heredity (parent(s), sibling(s)); - or single allergic heredity AND cord blood IgE > 0.5 kU/l.

Isle of Wight 1994 (Continued)

	Exclusion criteria: - living outside research area; - prematurity; - moving from research area; - non-compliance with intervention; - non-compliance with participation in follow-up visits. Number of participants: 136 of which included in the intervention group: n = 67 and included in the control group: n = 69 See above	
Interventions	Multifaceted intervention on reducing exposure to HDM and encouragement of breast-feeding, strict dietary regimen for lactating mothers and delay of introducing child to allergenic solid foods until 9 months and stepwise standardised introduction from then on Control intervention: usual care	
Outcomes	Clinical outcomes as evaluated at regular visits by paediatric allergist: - diagnosis of asthma; - diagnosis of constitutional eczema (SCORAD); - allergic rhinitis; - food intolerance; - positive SPT single allergen (HDM, cat dander, dog dander, molds, cow’s milk, egg, wheat); - positive SPT > 1 allergen; - any allergy.	
Notes		
<i>Risk of bias</i>		
Item	Authors’ judgement	Description
Adequate sequence generation?	Unclear	B unclear
Allocation concealment?	Yes	A adequate
Incomplete outcome data addressed? All outcomes	No	C inadequate
Free of selective reporting?	Yes	A adequate
Blinding of participants?	No	C inadequate
Blinding of healthcare provider?	Yes	A adequate

Isle of Wight 1994 (Continued)

Blinding of outcome assessor?	Yes	A adequate
Balanced at baseline?	No	C inadequate
Specification of inclusion and exclusion criteria?	Yes	A adequate
Specification of primary outcome?	Yes	A adequate

Isle of Wight 1997

Methods	See above
Participants	See above
Interventions	See above
Outcomes	Clinical outcomes as evaluated at regular visits by paediatric allergist: - diagnosis asthma; - diagnosis constitutional eczema; - allergy (any positive SPT); - definite allergy (allergy symptoms plus positive SPT); - rhinitis; - food Intolerance; - positive SPT.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	B unclear
Allocation concealment?	Yes	A adequate
Incomplete outcome data addressed? All outcomes	No	C inadequate
Free of selective reporting?	Yes	A adequate
Blinding of participants?	No	C inadequate
Blinding of healthcare provider?	Yes	A adequate

Isle of Wight 1997 (Continued)

Blinding of outcome assessor?	Yes	A adequate
Balanced at baseline?	No	C inadequate
Specification of inclusion and exclusion criteria?	Yes	A adequate
Specification of primary outcome?	Yes	A adequate

Isle of Wight 2003

Methods	See above
Participants	See above
Interventions	See above
Outcomes	Clinical outcome measures: - current asthma, defined as current wheeze plus BHR < 8 mg/ml; - current wheeze as reported in ISAAC questionnaire; - nocturnal cough as reported in ISAAC questionnaire; - exercise induced wheeze as reported in ISAAC questionnaire; - BHR defined as PC20 < 8 mg/ml. Lung function results: - FEV1 (% predicted); - Peak flow (% predicted); - FEF25-75 (% predicted); - bronchial responsiveness (max change in FEV1 divided by cumulative dose of meta-choline given for each subject); - skin test outcome, house dust mite, grass pollen, tree pollen, cat, any aeroallergen, cow's milk, peanut, any food allergen, any allergen (atopy); - IgE outcome: total IgE (geometric means (SD), means difference and 95% CI); - IgE inhalant screen positive.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	B unclear
Allocation concealment?	Yes	A adequate

Isle of Wight 2003 (Continued)

Incomplete outcome data addressed? All outcomes	No	C inadequate
Free of selective reporting?	Yes	A adequate
Blinding of participants?	No	C inadequate
Blinding of healthcare provider?	Yes	A adequate
Blinding of outcome assessor?	Yes	A adequate
Balanced at baseline?	No	C inadequate
Specification of inclusion and exclusion criteria?	Yes	A adequate
Specification of primary outcome?	Yes	A adequate

Mallet 1992

Methods	Longitudinal birth cohort study with follow up of children from birth to 4 years Patients were blinded, provider was naive; of providers only the paediatrician was not blind nor naive. Blinding of outcome assessor unclear. n = 38 drop-outs at age 2 years of which n = 14 in the prophylactic group and 24 in the control group. At 4 years there were another 14 drop-outs of which 8 in the prophylactic group and 7 in the control group.
Participants	Recruitment of n = 92 in the intervention group and n = 85 controls in 1 maternity hospital of infants at high risk of developing atopy on grounds of history of atopic disease in first degree family members, confirmed by medical records Infants were randomly assigned to 1 of 2 groups: prophylactic group (n = 92) or control group (n = 85)
Interventions	The prophylactic group received a formula based on a casein hydrolysate for 4 months (supplied by the hospital) either exclusively or as a complement to or substitute for human milk. No other food was allowed, including fruit juice. No specific instructions were given regarding the mother's diet during pregnancy and breastfeeding. Parents and their physicians were given an observation sheet to record anthropometric data, significant clinical reactions (cutaneous, digestive or respiratory) and paediatricians knew which formula was fed to the infant. Control group intervention: The same as the prophylactic group intervention with the only difference the type of formula supplied. The control group infants received adapted cow's milk formula.

Mallet 1992 (Continued)

Outcomes	Clinical outcome as identified at clinical assessment: - diagnosis asthma (tic bronchitis), defined as mild, 2 to 4 occurrences yearly, severe defined as more than 4 occurrences yearly; - diagnosis eczema: - mild eczema defined as less than 4 patches of eczema; - moderate eczema; - drug-resistant eczema; - severe eczema; - obvious cow's milk protein allergy verified by criteria of type I reagenic allergy of malabsorption; - total IgE levels were measured in cord blood at birth and in blood obtained by vena puncture at 4 and 12 months of age. If above normal levels were detected, cow's milk protein specific IgE was measured.	
Notes	Mild and severe asthma (tic) bronchitis as described in article were cumulatively included in 'outcome asthma defined as doctor diagnosis in children aged < five years) as the described outcome was result of clinical assessment	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	B unclear
Allocation concealment?	Yes	A adequate
Incomplete outcome data addressed? All outcomes	No	C inadequate
Free of selective reporting?	Yes	A adequate
Blinding of participants?	Yes	A adequate
Blinding of healthcare provider?	No	C inadequate
Blinding of outcome assessor?	Yes	A adequate
Balanced at baseline?	Unclear	B unclear
Specification of inclusion and exclusion criteria?	Yes	A adequate
Specification of primary outcome?	Yes	A adequate

Methods	Longitudinal birth cohort intervention study with follow up of children from pregnancy to 8 years Patients (not clear if blinded or naive). Outcome assessors and providers were blinded. Number of drop-outs at 3 years of age: 52 (n = 17 in intervention group and n = 35 in control group)
Participants	All pregnant women and their partners in 654 antenatal clinics were screened for eligibility at 8 to 10 weeks pregnancy by SPT and structured questionnaire Included were n = 145 in the intervention group and n = 146 controls Inclusion criteria: - high risk of developing allergic disease (both parents atopic); - no pet cat or dog at home. Exclusion criteria: - inclusion criteria not fulfilled Number of included participants (minus infants withdrawn before birth): 256 in the environmental control RCT, of which n = 133 in the active group and n = 123 in the control group
Interventions	Intervention: - environmental control measures consisting of use of mite impermeable mattress encasings for parental bed from pregnancy on; - use of mite impermeable mattress cover for child's bed; - advice to hot wash bed linen weekly; - high filtration vacuum cleaner, washable soft toy and crib mattress provided; - carpets of child's bedroom were removed and replaced by smooth floor coverings; - carpets and sofas were 3 monthly treated with anti-mite fluid. Placebo intervention: usual care
Outcomes	Clinical outcomes: - asthma, physician diagnosed; - wheeze ever; - current wheeze (last 3 months) - wheeze age 1 to 3 years; - wheezy attacks requiring medication; - > 3 episodes of severe wheeze; - wheeze after exertion; - night-time cough; - cough apart from colds; - cough after exertion; - cough with excitement; - current asthma medication; - rhinitis; - current eczema; - SPT positive (Der p1, Fel d1, Can f1, mixed grasses, milk, egg, overall minimally sensitised for 1 allergen tested); - IgE (Der p, Fel d1, Can f1, milk, egg, overall minimally sensitised for one allergen tested);

nacMAAS 2004 (Continued)

	- lung function (specific airway resistance sRaw).	
Notes	Outcome 'current wheeze as parental reported' included in current meta-analysis as 'current wheeze (last 3 months)'	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	B unclear
Allocation concealment?	Yes	A adequate
Incomplete outcome data addressed? All outcomes	No	C inadequate
Free of selective reporting?	Yes	A adequate
Blinding of participants?	No	C inadequate
Blinding of healthcare provider?	Yes	A adequate
Blinding of outcome assessor?	Yes	A adequate
Balanced at baseline?	Unclear	B unclear
Specification of inclusion and exclusion criteria?	Yes	A adequate
Specification of primary outcome?	Yes	A adequate

PIAMA 2006

Methods	Longitudinal birth cohort intervention study with follow up of children from pregnancy to 2 years Patients, providers and outcome assessors were blinded Number of drop-outs at age 4 years: n = 207, of which n = 92 in the active group and n = 115 in the placebo group
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PIAMA 2006 (Continued)

Participants	Recruitment n = 416 in the intervention group and n = 394 controls Pregnant women in their third trimester of pregnancy were contacted with help of midwives and obstetric clinics Inclusion criteria: - pregnant women in their third trimester of pregnancy; - allergic mother on grounds of questionnaire data. Exclusion criteria: - not described Number of participants in the intervention study: n = 810, of which n = 416 in the active group and n = 394 in the placebo group	
Interventions	monofaceted intervention on reducing exposure to HDM allergens Intervention: - active HDM allergen impermeable encasing were supplied for mattress and pillow of child and parents bed; - instructions on washing bed linen at HDM killing temperature; - families were supplied with a brochure of the Dutch Asthma Foundation (NAF) on allergen avoidance. Placebo group intervention: Only difference with active intervention was the placebo group received placebo encasings but brochure and washing advice was the same	
Outcomes	Clinical outcomes: - 4 wheezing categories: 1 never wheezed, 2 early transient wheeze, 3 persistent wheeze, 4 late wheeze; - wheeze in 4th year; - night-time cough in 4th year; - atopic dermatitis in 4th year; - rhinitis in 4th year; - rhinitis and eye symptoms in 4th year; - IgE outcome as measured at 4 years of age: total IgE IU/ml, specific IgE against HDM, cat, dog, grass pollen, birch pollen >= 0.35 IU/ml/total.	
Notes	Data of described study-outcome 'wheezing in 4th year' included in outcome 'current wheezing' in current meta-analysis	
Risk of bias		
Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	B unclear
Allocation concealment?	Yes	A adequate

PIAMA 2006 (Continued)

Incomplete outcome data addressed? All outcomes	Yes	A adequate
Free of selective reporting?	Yes	A adequate
Blinding of participants?	Yes	A adequate
Blinding of healthcare provider?	Yes	A adequate
Blinding of outcome assessor?	Yes	A adequate
Balanced at baseline?	No	C inadequate
Specification of inclusion and exclusion criteria?	Yes	A adequate
Specification of primary outcome?	Yes	A adequate

PREVASC 2005

Methods	Longitudinal birth cohort intervention study with follow up of children from prenatal age until 6 years Pre-randomisation of participants. Patients in intervention group informed, not blinded, patients in control group were blinded. GP not blinded nor naive, outcome assessors blinded Number of drop-outs at age 2 years n = 33, of which n = 20 in intervention group and n = 13 in control group, all during prenatal or delivery period due to miscarriages, still birth, long lasting hospitalisation or moving. No data on study outcome were collected.
Participants	Recruitment of n = 242 in the intervention group and n = 234 controls: GPs and midwives informed pregnant women and inclusion criteria were checked by GP and screening questionnaires Inclusion criteria: - pregnant women included during first or second trimester of pregnancy; minimally one first degree relative of child is diagnosed as being asthmatic as reported by GPs; - living in the south of The Netherlands. Exclusion criteria: - major language problem; - moving outside the country; - severe illness/malformation child. Number of participants followed up: n = 443, of which n = 222 in the intervention group and n = 221 in the usual care group

Interventions	Multifaceted intervention on reducing exposure to HDM, pets, ETS and encouragement of breastfeeding for 6 months and/or hypo-allergenic formula as well as delay of introduction of solid foods Control group intervention: Usual care, no study intervention
Outcomes	Clinical outcome measures: - asthma, as diagnosed by GP; - asthma symptoms: wheezing (with or without fever), nocturnal cough in the absence of cold minimally once a week, shortness of breath (dyspnoea) as reported by GPs and as reported by parents in weekly reports; - constitutional eczema, as diagnosed by GP; - total and specific IgE level (HDM, cat, dog) as measured in blood at age 2 years; - atopy defined as IgE level for HDM, cat or dog allergen > 10 U/ml.
Notes	GP diagnosis of asthma included in outcome 'current asthma (defined as doctor diagnosis) in children aged < 5 years' Current respiratory symptoms: current wheezing, current nocturnal cough and current dyspnoea as reported by parents in weekly reports included in current meta-analyses

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	A adequate
Allocation concealment?	Yes	A adequate
Incomplete outcome data addressed? All outcomes	Yes	A adequate
Free of selective reporting?	Yes	A adequate
Blinding of participants?	No	C inadequate
Blinding of healthcare provider?	No	C inadequate
Blinding of outcome assessor?	Yes	A adequate
Balanced at baseline?	Yes	A adequate
Specification of inclusion and exclusion criteria?	Yes	A adequate

PREVASC 2005 (Continued)

Specification of primary outcome?	Yes	A adequate
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SPACE 2004

Methods	Longitudinal birth cohort intervention study with follow up of children from pregnancy to 2 years Patients and providers were kept naive, outcome assessors blinded; Number of drop-outs at age 2 years: n = 133, of which 58 in the intervention group and 75 in the control group
Participants	Recruitment of n = 349 in the intervention group and n = 347 controls: all pregnant women at three centres (in Germany, Austria and UK) were screened on eligibility for inclusion in a 12-month period. The majority of women were approached during routine visits to obstetric ward or antenatal clinics during pregnancy. ISAAC-questionnaires and questionnaires of the MAS study were used to determine the family history of atopic disorders in parents or siblings. If a positive answer on atopy questions was reported a SPT or blood test for specific IgE was carried out on at least one parent, to determine their allergic sensitisation (HDM allergens (Der p1 and Der f1), grass mixture, cat dander). If subject did not comply to the SPT they had their blood tested for IgE total and specific Randomisation was in 2-week periods and infants were allocated according to the expected date of delivery or the actual date of delivery if recruited postnatally Participants: n = 696, of which n = 349 in the intervention group and n = 347 in the control group
Interventions	monofaceted intervention, primarily aimed at HDM exposure reduction: - at birth, mite impermeable mattress encasings were provided for the infant's bed as well as their parent's bed; - in addition they received information on allergy and allergen reducing measures including written encouragement to avoid food allergens; - breastfeeding until 3 months of age or otherwise use of hypoallergenic formula. - cow's milk formula was recommended to be avoided until 6 months. - cow's milk other than formula as well as egg and fish were advised to be avoided until the child aged 12 months; - solid foods should be delayed until 4 to 6 months and wheat should be avoided until 6 months; - peanuts and tree nuts should not be introduced until 3 years of age; - information on ventilation and ETS exposure reduction and not allowing pets in the bedroom was provided. Placebo intervention: - a booklet was provided, containing more basic information on the measures the intervention group was advised on; - no placebo mattress encasings were provided.

Outcomes	Clinical outcomes: - asthma (parental reported); - recurrent wheezing (ISAAC questionnaire); - nocturnal cough (ISAAC questionnaire). Other symptoms: - rhinitis (ISAAC questionnaire); - sensitisation to mites (positive SPT or specific IgE against Der p1 or Der f1 > 1.43 kU/l); - any allergy (defined as asthma or nocturnal cough or recurrent wheeze or eczema or rhinitis in the first 24 months of life); - atopic eczema (parental reported doctor's diagnosis).	
Notes	Article SPACE G Halmerbauer used for additional information on study design	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Adequate sequence generation?	Yes	A adequate
Allocation concealment?	Yes	A adequate
Incomplete outcome data addressed? All outcomes	No	C inadequate
Free of selective reporting?	Yes	A adequate
Blinding of participants?	Yes	A adequate
Blinding of healthcare provider?	Yes	A adequate
Blinding of outcome assessor?	Yes	A adequate
Balanced at baseline?	Unclear	B unclear
Specification of inclusion and exclusion criteria?	Yes	A adequate
Specification of primary outcome?	Yes	A adequate

Zeiger 1989

Methods	Longitudinal birth cohort intervention study with follow up of children from pregnancy to 7 years Patients were blinded, as well as providers and outcome assessors Number of drop-outs at age 2 years: n = 50 in the intervention group and n = 13 controls
Participants	Recruitment of n = 153 in the intervention group and n = 198 controls by informing pregnant women suggestive of atopy (questionnaire data filled in during a routine obstetrical visit) were invited with their partner to a study presentation Inclusion criteria: - at least 1 parent has a history of atopic disorder; - specific IgE by skin or RAST testing. Skin tested of mothers to foods and inhalants 4 months postpartum. Exclusion criteria: - inclusion criteria not fulfilled Number of participants: 288 Intervention group n = 103 and control group n = 185
Interventions	monofaceted intervention study on reducing exposure to food allergens. Both groups were encouraged to breastfeed their child 4 to 6 months and parents received intensive education reducing environmental allergens and ETS Prophylactic group diet: During last trimester of pregnancy and while breastfeeding, women were instructed to avoid all dairy milk, egg and peanut products, concentrated soy foods (tofu) and limit wheat to no more than 2 servings daily, with other grains to fulfil the cereal and starch requirements. Dietary instructions provided by dieticians before the third trimester. If breastfeeding was supplemented or stopped, a casein hydrolysate formula with low sensitisation potential was to be fed until 12 months of age. Introducing solid foods at 6 months conformed to a standardised stepwise introduction protocol from 6 months to 3 years. Control group diet: Pregnant and lactating women were encouraged to follow standard diets as provided by the Kaiser Permanente Obstetric Department. A cow's milk based whey infant formula was provided for supplementation or weaning first year. Solid foods introduced at 4 months (cereal) followed by stepwise introduction of vegetables, fruits and egg yolks, meat and whole cow's milk until 12 months.
Outcomes	Clinical outcomes at 2 years: - definite asthma defined as 3 episodes of physician documented wheezing episodes occurred unassociated with foreign body, congenital abnormality, croup, aspiration, or gastro-oesophageal reflux; - allergic asthma defined as at least 1 episode of wheezing triggered by foods or aeroallergens associated with concomitant specific IgE; - probable asthma, defined as 2 episodes of wheezing unassociated with foreign body, croup, congenital abnormality, aspiration or gastro-oesophageal reflux; - gastrointestinal disease; - atopic dermatitis;

Zeiger 1989 (Continued)

	- allergic rhinitis; - any atopic disorder (definite and probable).	
Notes	Definite asthma outcome as reported included in current meta-analysis Although cumulative as well as period prevalences were reported, only period prevalences were included in this meta-analysis	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Adequate sequence generation?	Yes	A adequate
Allocation concealment?	Yes	A adequate
Incomplete outcome data addressed? All outcomes	No	C inadequate
Free of selective reporting?	Yes	A adequate
Blinding of participants?	Unclear	B unclear
Blinding of healthcare provider?	Yes	A adequate
Blinding of outcome assessor?	Yes	A adequate
Balanced at baseline?	Unclear	B unclear
Specification of inclusion and exclusion criteria?	Yes	A adequate
Specification of primary outcome?	Yes	A adequate

Zeiger 1992

Methods	See above Number of drop-outs at age 4 years: n = 18 in the prophylactic group and 45 in the control group
Participants	See above
Interventions	See above

Outcomes	Clinical outcomes: - asthma, defined as physician documented lower respiratory condition with characteristic reversible bronchospasm, occurring at least twice and unassociated with other anatomic congenital or immunologic causes; - atopic dermatitis, defined as at least 3 of the following criteria: pruritis, typical morphology and distribution, tendency toward chronicity or recurrence, concurrent specific IgE; - urticaria/angioedema, defined as a pruritic eruption with typical morphologic appearance reported by physician or parent with or without incriminating agents identified; - allergic rhinitis, defined as a nasal condition with characteristic sneezing, itching and/or rhinorrhoea with concurrent specific IgE and nasal eosinophilia; - food allergy, defined as food-specific IgE with symptoms consistent with atopic dermatitis, urticaria/angioedema triggered at least twice by a specific food, GI allergy induced on at least 2 occasions by a specific food.	
Notes	Definite asthma outcome as reported included in current meta-analysis. Although cumulative as well as period prevalences were reported, only period prevalences were included in this meta-analysis.	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Adequate sequence generation?	Yes	A adequate
Allocation concealment?	Yes	A adequate
Incomplete outcome data addressed? All outcomes	No	C inadequate
Free of selective reporting?	Yes	A adequate
Blinding of participants?	Unclear	B unclear
Blinding of healthcare provider?	Yes	A adequate
Blinding of outcome assessor?	Yes	A adequate
Balanced at baseline?	Unclear	B unclear
Specification of inclusion and exclusion criteria?	Yes	A adequate
Specification of primary outcome?	Yes	A adequate

Zeiger 1995

Methods	See above Number of drop-outs at age 7 years: n = 44 in the prophylactic group and 79 in the control group
Participants	See above
Interventions	See above
Outcomes	Clinical outcomes at 7 years: - diagnosis asthma: defined as physician documented lower respiratory disorder with reversible bronchospasm, occurring at least twice and unassociated with other anatomic, congenital or immunologic causes; - diagnosis atopic dermatitis, defined as an eczematous eruption associated with at least 3 of the following 4 criteria: 1) pruritis, 2) typical appearance and distribution, 3) tendency toward chronicity or recurrence and 4) concurrent specific IgE; - urticaria/angioedema, defined as a pruritic eruption or swelling with typical appearance observed by physician or parent irrespective of cause; - allergic rhinitis, defined as a nasal condition with characteristic symptoms of sneezing, itching and/or rhinorrhoea with concurrent specific IgE and nasal eosinophils; - food allergy, defined as atopic dermatitis, urticaria/angioedema or diarrhoea/vomiting occurring on at least 2 occasions or anaphylaxis induced by a specific food with concurrent food-specific IgE.
Notes	Although cumulative as well as period prevalences were reported, only period prevalences were included in this meta-analysis

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	A adequate
Allocation concealment?	Yes	A adequate
Incomplete outcome data addressed? All outcomes	No	C inadequate
Free of selective reporting?	Yes	A adequate
Blinding of participants?	Unclear	B unclear
Blinding of healthcare provider?	Yes	A adequate
Blinding of outcome assessor?	Yes	A adequate

Zeiger 1995 (Continued)

Balanced at baseline?	Unclear	B unclear
Specification of inclusion and exclusion criteria?	Yes	A adequate
Specification of primary outcome?	Yes	A adequate

AF = artificial formula

BHR = bronchial hyper responsiveness

CI = confidence interval

ETS = environmental tobacco smoke

FEF25-75 = mid forced expiratory flow

FEV1 = forced expiratory volume in 1 second

FOT = Forced Oscillation Technique

GP = General Practitioner

HDM = house dust mite

HM = human milk

IgE = immune globulin E

PC20 = 20% reduction of FEV1 after metacholine/histamine

Rrs = resistance of respiratory system

SPT = skin prick test

sRaw = specific airway resistance

Characteristics of excluded studies [ordered by study ID]

Arshad 1992	Results of the Isle of Wight study on clinical outcome of children at 1 year of age described. Inclusion criterion 'description of clinical effect on children aged minimally 2 years' was not fulfilled.
Boggs 2003	No clinical effect described
Bottcher 2002	No RCT described
Brunekreef 2002	Design article of PIAMA study in which results of natural history part of PIAMA on allergen exposure are described. No clinical effect described.
Chan-Yeung 2002	Results of intervention Canadian Allergy and Asthma Prevention study on allergen reducing outcome. No clinical effect described.
Chandra 1997	Excluded because investigations by Chandra's university (Memorial University of Newfoundland) and the Canadian Broadcasting Corporation strongly suggest that the published data may have been fabricated.

(Continued)

CMA 2005	No RCT described
Custovic 2000a	Only results of intervention nacMAAS study on allergen reducing outcome reported. No clinical effect described.
Custovic 2000b	Results described of nacMAAS study on allergen reducing outcome. No clinical effect described.
Custovic 2001	Results of nacMaas study on clinical outcome of children at 1 year of age described. Inclusion criterion 'description of clinical effect on children aged minimally two years' was not fulfilled.
Dunstan 2003	No allergen reducing intervention studied. No clinical effect described.
Johnstone 1966	Study on clinical effectiveness of food allergen reducing intervention (soy formula) that seemed to fit all inclusion criteria but was excluded because at least 1 of the items of quality assessment on which we based an inclusion criterion was unfulfilled (outcome assessor was not blinded and allocation concealment was not clear)
Kalliomaki 2001	Study on clinical effectiveness of probiotics intervention, no allergen reduction and no asthma outcome
Kjellman 1979	Study on clinical effectiveness of food allergen reducing intervention (soy formula) that seemed to fit all inclusion criteria but was excluded because at least one of the items of quality assessment on which we based an inclusion criterion was unfulfilled (outcome assessor was not blinded and allocation concealment was not clear).
Koopman 2002	Study on clinical effectiveness of monofaceted house dust mite reducing intervention that fitted all inclusion criteria but was excluded because no point prevalences were described nor supplied
Marini 1996	Multifaceted intervention study on primary prevention of atopic manifestation but the outcomes as selected for current review are not described
Marks 2006	CAPS study dietary intervention part in which no allergen reducing manipulation so inclusion criteria not fulfilled for this part of the study. The house dust mite reducing part of CAPS intervention as described in this article is however included.
Mihrshahi 2001	Article on design and research protocol of CAPS study. No clinical effect described.
Peat 2004	CAPS study dietary intervention part in which no allergen reducing manipulation so inclusion criteria not fulfilled for this part of the study. The house dust mite reducing part of CAPS intervention as described in this article is however included.
Saارين 1979	Article is not a RCT; a natural history study of breastfeeding
Simpson 2003	Allergen reducing results of nacMAAS study described. No clinical effect described.
Simpson 2004	Review of designs and allergen reducing outcome of RCTs on primary prevention of asthma in children. No clinical effect described.
van Strien 2002	Allergen exposure outcome in natural history part of PIAMA study reported. No clinical effect described.

RCT = randomised controlled trial

DATA AND ANALYSES

Comparison 1. Current diagnosis asthma ITT

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Multifaceted intervention	6		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Current diagnosis asthma defined as doctor diagnosis at age 2 years	3	1157	Odds Ratio (M-H, Random, 95% CI)	0.71 [0.53, 0.95]
1.2 Current diagnosis asthma defined as doctor diagnosis at age 4 years	1	136	Odds Ratio (M-H, Random, 95% CI)	0.56 [0.26, 1.23]
1.3 Current diagnosis asthma defined as respiratory symptoms plus BHR and/or reversibility at age 7 years	1	545	Odds Ratio (M-H, Random, 95% CI)	0.52 [0.31, 0.89]
1.4 Current diagnosis asthma defined as respiratory symptoms plus BHR and/or reversibility at age 8 years	1	136	Odds Ratio (M-H, Random, 95% CI)	0.54 [0.17, 1.70]
1.5 Current diagnosis asthma defined as doctor diagnosis at age < 5 years last reported	3	1157	Odds Ratio (M-H, Random, 95% CI)	0.72 [0.54, 0.96]
1.6 Current diagnosis asthma defined as respiratory symptoms plus BHR and/or reversibility at age >= 5 yrs last reported	2	681	Odds Ratio (M-H, Random, 95% CI)	0.52 [0.32, 0.85]
2 Mono-faceted intervention	8		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Current diagnosis asthma defined as doctor diagnosis at age 2 years	3	1224	Odds Ratio (M-H, Random, 95% CI)	0.88 [0.48, 1.64]
2.2 Current diagnosis asthma defined as doctor diagnosis at age 3 years	2	872	Odds Ratio (M-H, Random, 95% CI)	0.84 [0.41, 1.71]
2.3 Current diagnosis asthma defined as doctor diagnosis at age 4 years	2	528	Odds Ratio (M-H, Random, 95% CI)	1.09 [0.60, 1.98]
2.4 Current diagnosis asthma defined as doctor diagnosis at age 5 years	1	616	Odds Ratio (M-H, Random, 95% CI)	0.86 [0.57, 1.29]
2.5 Current diagnosis asthma defined as respiratory symptoms plus BHR and/or reversibility at age 7 years	1	357	Odds Ratio (M-H, Random, 95% CI)	0.73 [0.40, 1.35]

2.6 Current diagnosis asthma defined as doctor diagnosis at age < 5 years last reported	5	2131	Odds Ratio (M-H, Random, 95% CI)	1.12 [0.76, 1.64]
2.7 Current diagnosis asthma defined as respiratory symptoms plus BHR and/or reversibility at age >= 5 yrs last reported	2	967	Odds Ratio (M-H, Random, 95% CI)	0.83 [0.59, 1.16]

Comparison 2. Current wheezing parental reported ITT

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Multifaceted	4		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Current wheezing parental reported at age 2 years	2	1021	Odds Ratio (M-H, Random, 95% CI)	0.81 [0.34, 1.90]
1.2 Current wheezing parental reported at age 7 & 8 years	2	681	Odds Ratio (M-H, Random, 95% CI)	0.52 [0.30, 0.88]
1.3 Current wheezing parental reported data last reported	3	1157	Odds Ratio (M-H, Random, 95% CI)	0.53 [0.35, 0.81]
2 Mono-faceted	4		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Current wheezing parental reported at age 3 years	2	907	Odds Ratio (M-H, Random, 95% CI)	0.93 [0.65, 1.35]
2.2 Current wheezing parental reported at age 4 years	1	810	Odds Ratio (M-H, Random, 95% CI)	1.01 [0.50, 2.02]
2.3 Current wheezing parental reported at age 5 years	1	616	Odds Ratio (M-H, Random, 95% CI)	0.88 [0.60, 1.28]
2.4 Current wheezing parental reported data last reported	3	1717	Odds Ratio (M-H, Random, 95% CI)	0.90 [0.67, 1.22]

Comparison 3. Current nocturnal cough parental reported ITT

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Multifaceted	3		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Current nocturnal cough parental reported at age 2 years	1	443	Odds Ratio (M-H, Random, 95% CI)	0.71 [0.47, 1.08]
1.2 Current nocturnal cough parental reported at age 7 & 8 years	2	681	Odds Ratio (M-H, Random, 95% CI)	0.63 [0.21, 1.92]
1.3 Current nocturnal cough parental reported data last reported	3	1157	Odds Ratio (M-H, Random, 95% CI)	0.70 [0.42, 1.16]
2 Mono-faceted	3		Odds Ratio (M-H, Random, 95% CI)	Subtotals only

2.1 Current nocturnal cough parental reported data last reported	3	1800	Odds Ratio (M-H, Random, 95% CI)	1.03 [0.77, 1.38]
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Comparison 4. Current dyspnoea parental reported ITT

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Multifaceted	1		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Current dyspnoea parental reported at age 2 years	1	476	Odds Ratio (M-H, Random, 95% CI)	1.18 [0.67, 2.08]

Comparison 5. Sensitivity analyses current asthma on treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Multifaceted interventions	5	1624	Odds Ratio (M-H, Random, 95% CI)	0.67 [0.52, 0.86]
1.1 < 5 years last reported	3	1039	Odds Ratio (M-H, Random, 95% CI)	0.73 [0.55, 0.98]
1.2 ≥ 5 years last reported	2	585	Odds Ratio (M-H, Random, 95% CI)	0.52 [0.32, 0.85]
2 Mono-faceted interventions	8	5232	Odds Ratio (M-H, Random, 95% CI)	1.02 [0.85, 1.22]
2.1 2 years	3	967	Odds Ratio (M-H, Random, 95% CI)	1.13 [0.42, 3.10]
2.2 3 years	2	798	Odds Ratio (M-H, Random, 95% CI)	0.83 [0.42, 1.65]
2.3 4 years	2	349	Odds Ratio (M-H, Random, 95% CI)	1.25 [0.68, 2.32]
2.4 5 years	1	539	Odds Ratio (M-H, Random, 95% CI)	0.86 [0.57, 1.30]
2.5 7 years	1	165	Odds Ratio (M-H, Random, 95% CI)	1.15 [0.58, 2.29]
2.6 < 5 years last reported	5	1710	Odds Ratio (M-H, Random, 95% CI)	1.13 [0.77, 1.67]
2.7 ≥ 5 years last reported	2	704	Odds Ratio (M-H, Random, 95% CI)	0.93 [0.65, 1.32]

Comparison 6. Sensitivity analyses current dyspnoea on treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Multifaceted interventions	1	443	Odds Ratio (M-H, Random, 95% CI)	0.65 [0.39, 1.08]
1.1 last reported	1	443	Odds Ratio (M-H, Random, 95% CI)	0.65 [0.39, 1.08]

Comparison 7. Sensitivity analyses current nocturnal cough on treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Multifaceted interventions	3	1028	Odds Ratio (M-H, Random, 95% CI)	0.73 [0.46, 1.16]
1.1 Last reported	3	1028	Odds Ratio (M-H, Random, 95% CI)	0.73 [0.46, 1.16]
2 Mono-faceted interventions	3	1405	Odds Ratio (M-H, Random, 95% CI)	0.91 [0.67, 1.22]
2.1 Last reported	3	1405	Odds Ratio (M-H, Random, 95% CI)	0.91 [0.67, 1.22]

Comparison 8. Sensitivity analyses current wheezing on treatment

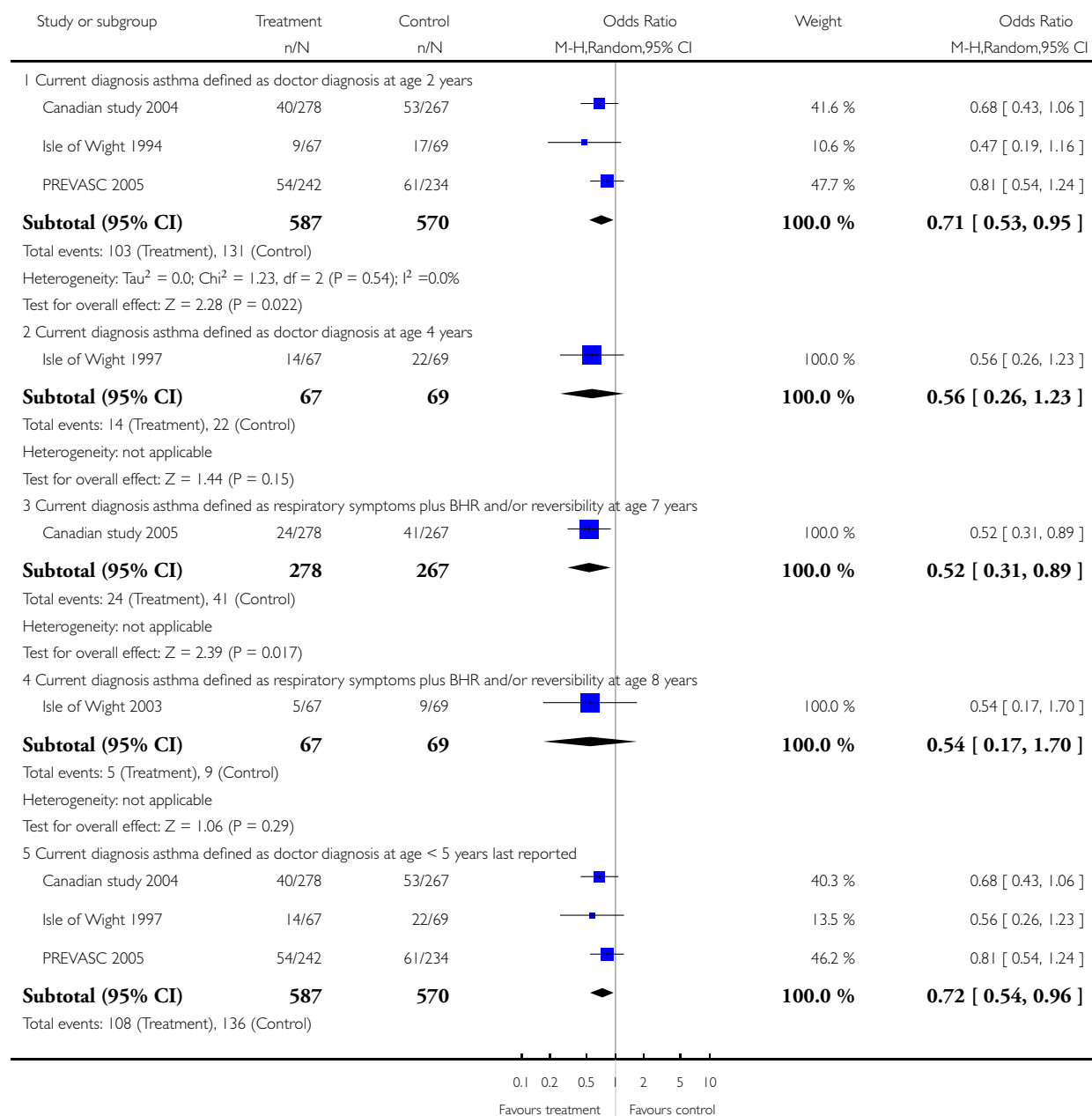
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Multifaceted interventions	4	2560	Odds Ratio (M-H, Random, 95% CI)	0.60 [0.45, 0.80]
1.1 2 years	2	947	Odds Ratio (M-H, Random, 95% CI)	0.89 [0.33, 2.40]
1.2 7 & 8 years	2	585	Odds Ratio (M-H, Random, 95% CI)	0.53 [0.31, 0.91]
1.3 Last reported	3	1028	Odds Ratio (M-H, Random, 95% CI)	0.54 [0.36, 0.83]
2 Mono-interventions	4	3316	Odds Ratio (M-H, Random, 95% CI)	0.87 [0.72, 1.06]
2.1 3 & 4 years	3	1396	Odds Ratio (M-H, Random, 95% CI)	0.89 [0.64, 1.23]
2.2 5 years	1	539	Odds Ratio (M-H, Random, 95% CI)	0.88 [0.59, 1.29]
2.3 Last reported	3	1381	Odds Ratio (M-H, Random, 95% CI)	0.85 [0.63, 1.15]

Analysis 1.1. Comparison 1 Current diagnosis asthma ITT, Outcome 1 Multifaceted intervention.

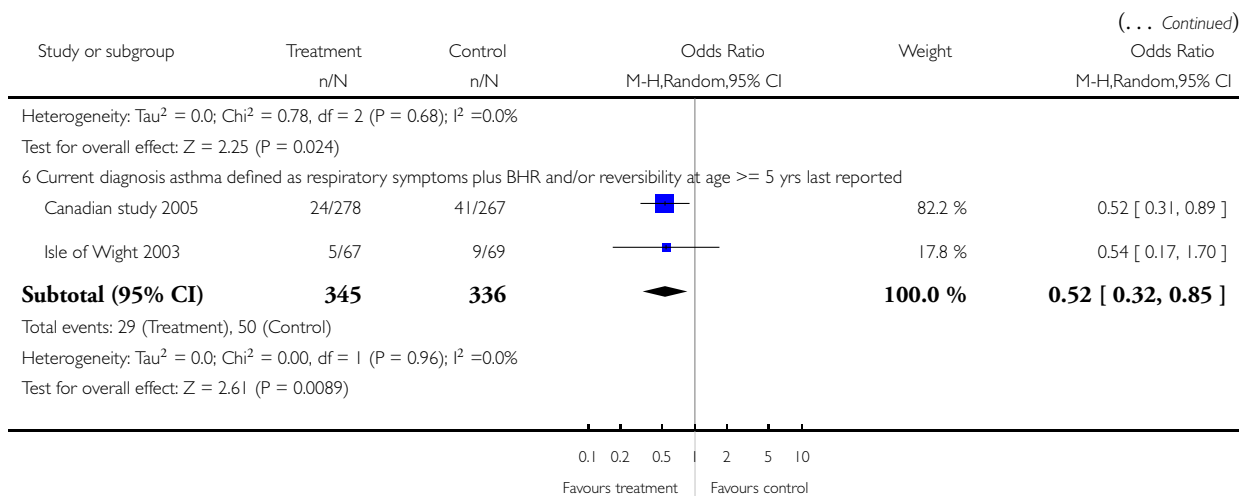
Review: Mono and multifaceted inhalant and/or food allergen reduction interventions for preventing asthma in children at high risk of developing asthma

Comparison: 1 Current diagnosis asthma ITT

Outcome: 1 Multifaceted intervention



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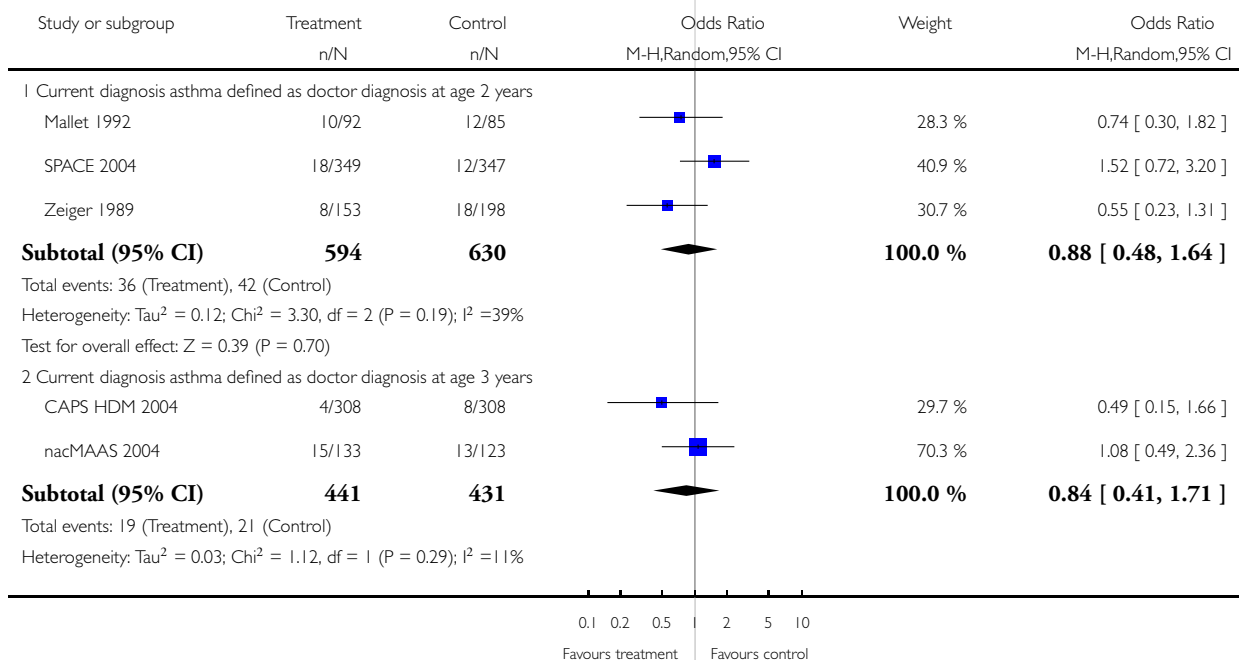


Analysis 1.2. Comparison 1 Current diagnosis asthma ITT, Outcome 2 Mono-faceted intervention.

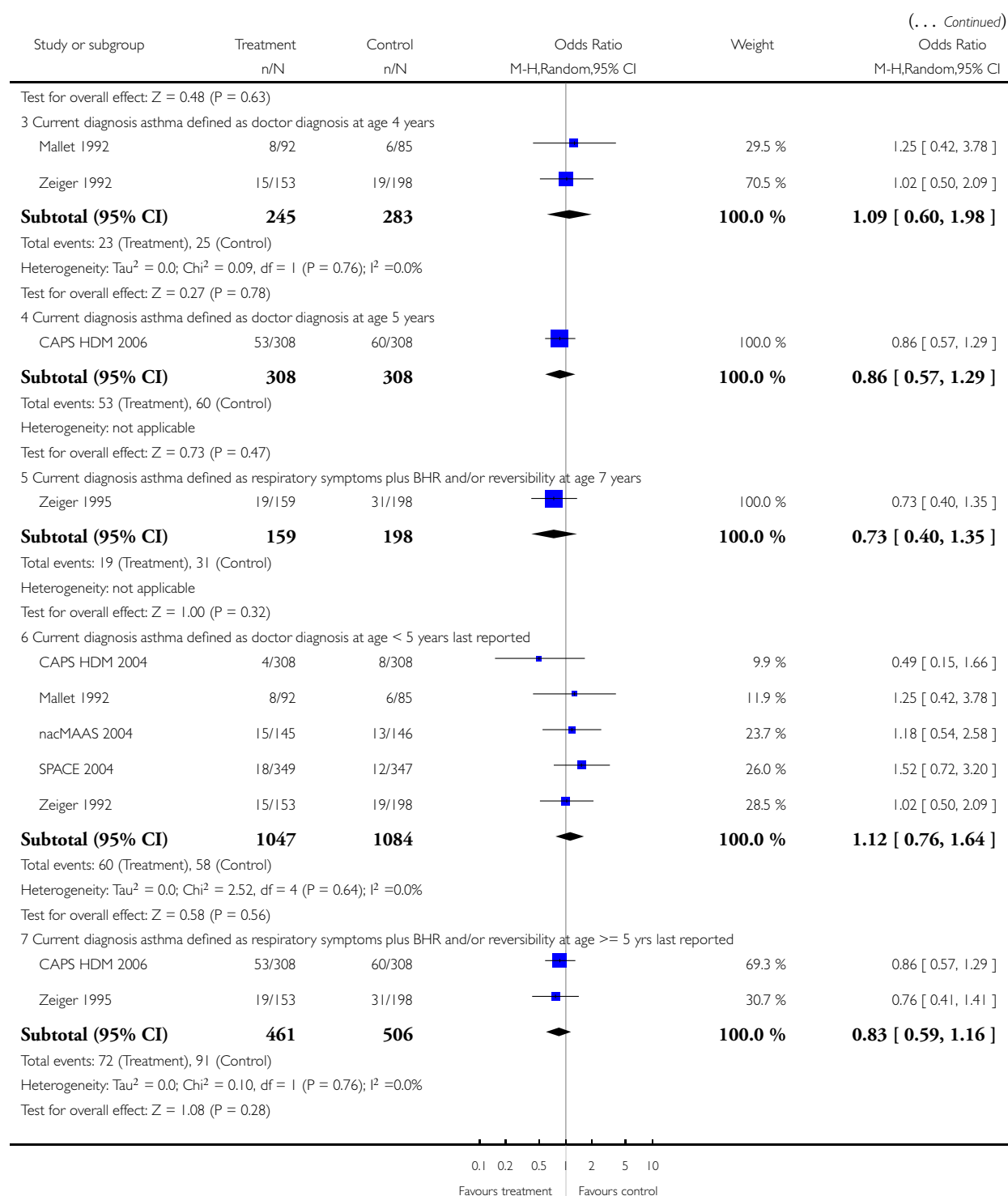
Review: Mono and multifaceted inhalant and/or food allergen reduction interventions for preventing asthma in children at high risk of developing asthma

Comparison: 1 Current diagnosis asthma ITT

Outcome: 2 Mono-faceted intervention



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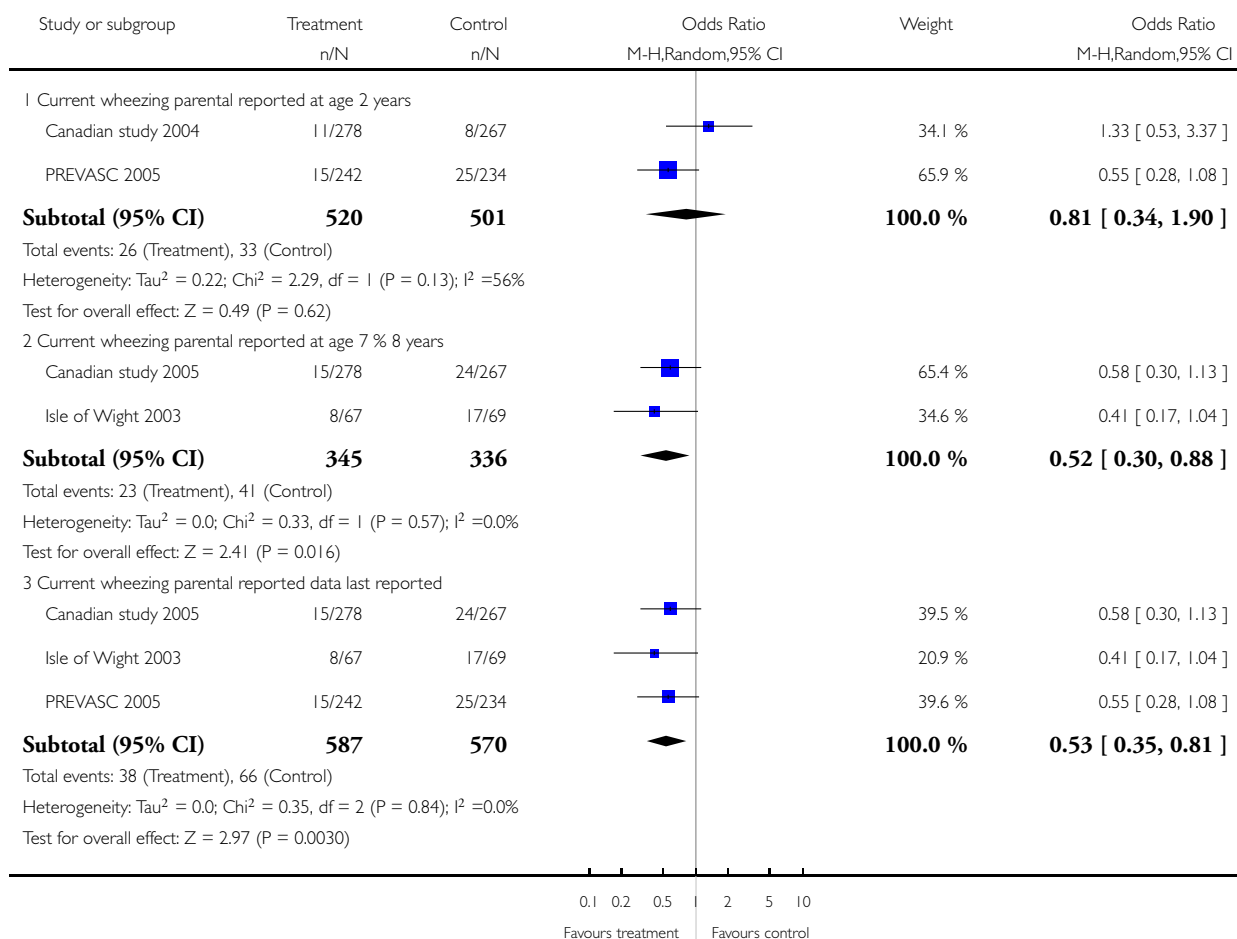


Analysis 2.1. Comparison 2 Current wheezing parental reported ITT, Outcome 1 Multifaceted.

Review: Mono and multifaceted inhalant and/or food allergen reduction interventions for preventing asthma in children at high risk of developing asthma

Comparison: 2 Current wheezing parental reported ITT

Outcome: 1 Multifaceted

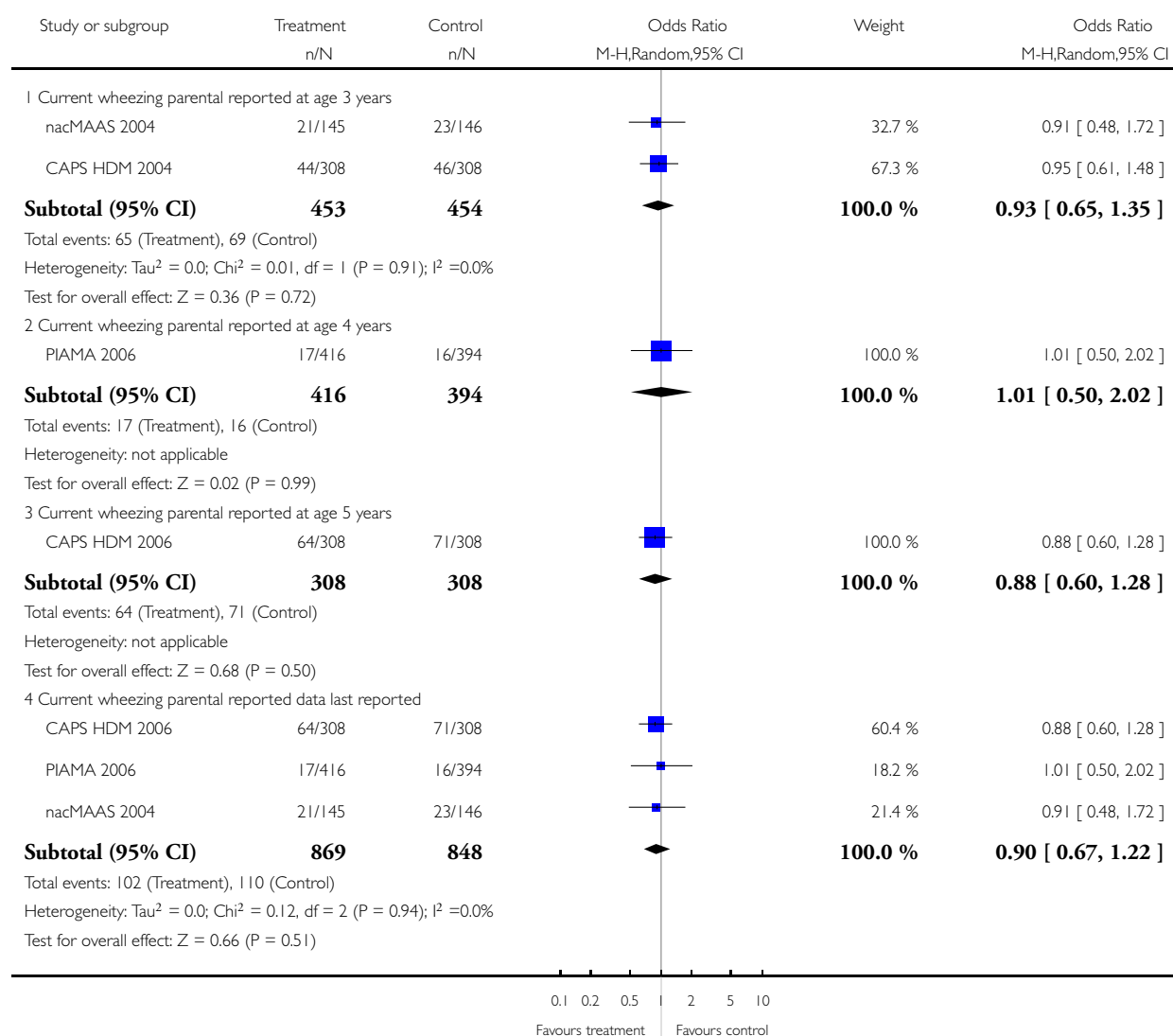


Analysis 2.2. Comparison 2 Current wheezing parental reported ITT, Outcome 2 Mono-faceted.

Review: Mono and multifaceted inhalant and/or food allergen reduction interventions for preventing asthma in children at high risk of developing asthma

Comparison: 2 Current wheezing parental reported ITT

Outcome: 2 Mono-faceted

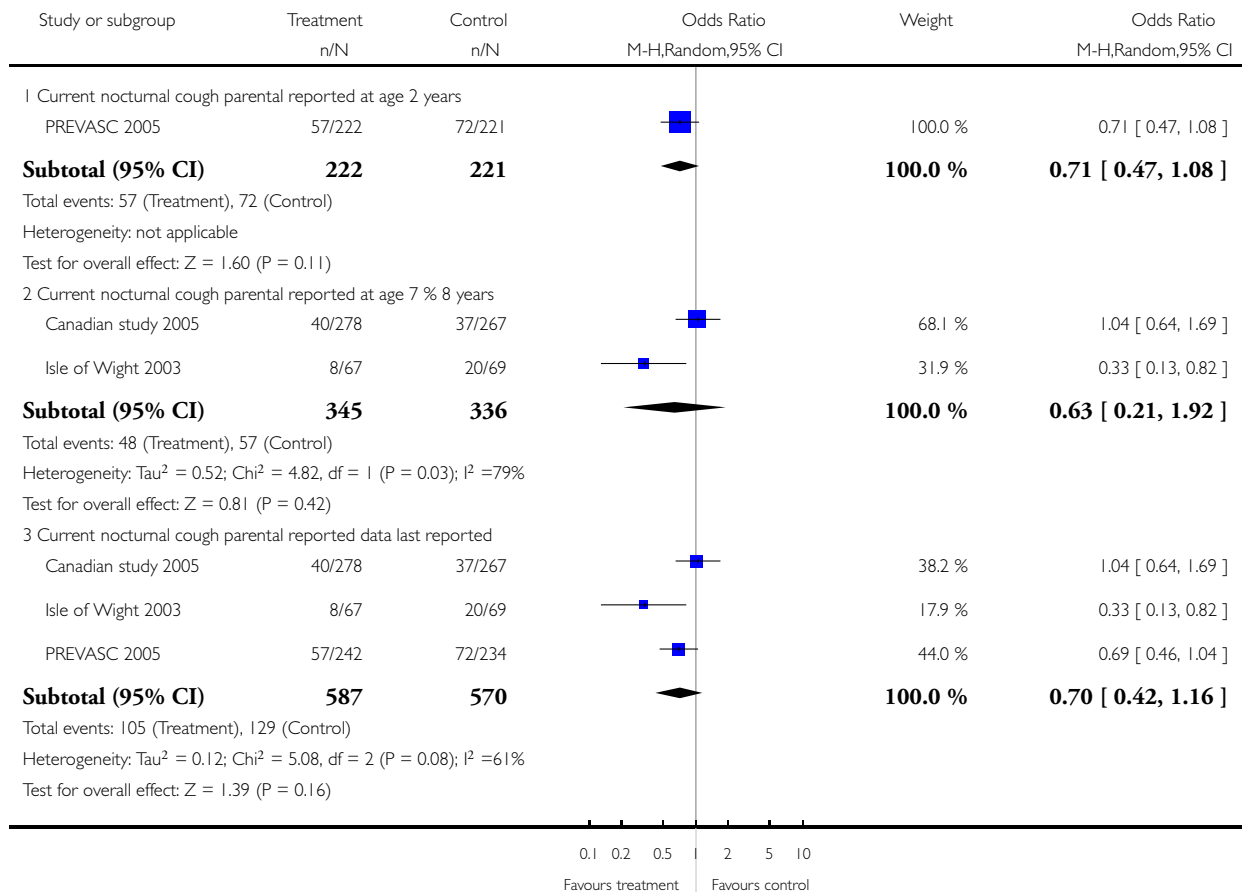


Analysis 3.1. Comparison 3 Current nocturnal cough parental reported ITT, Outcome 1 Multifaceted.

Review: Mono and multifaceted inhalant and/or food allergen reduction interventions for preventing asthma in children at high risk of developing asthma

Comparison: 3 Current nocturnal cough parental reported ITT

Outcome: 1 Multifaceted

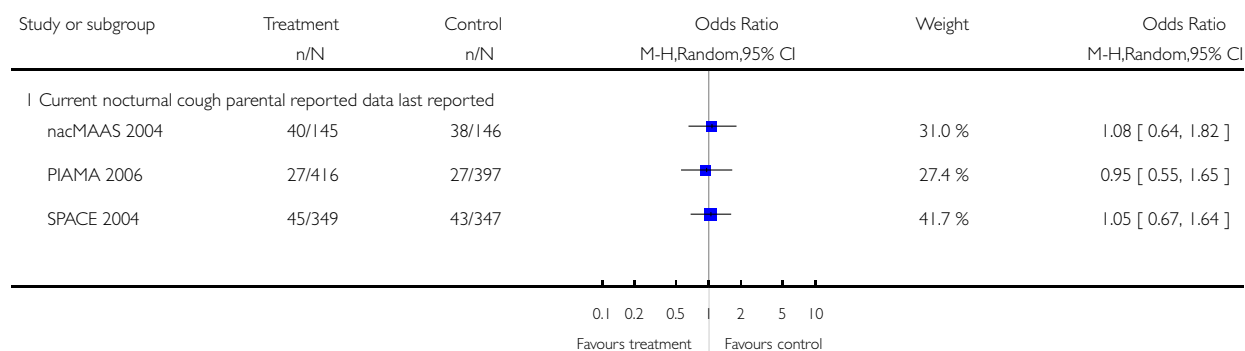


Analysis 3.2. Comparison 3 Current nocturnal cough parental reported ITT, Outcome 2 Mono-faceted.

Review: Mono and multifaceted inhalant and/or food allergen reduction interventions for preventing asthma in children at high risk of developing asthma

Comparison: 3 Current nocturnal cough parental reported ITT

Outcome: 2 Mono-faceted

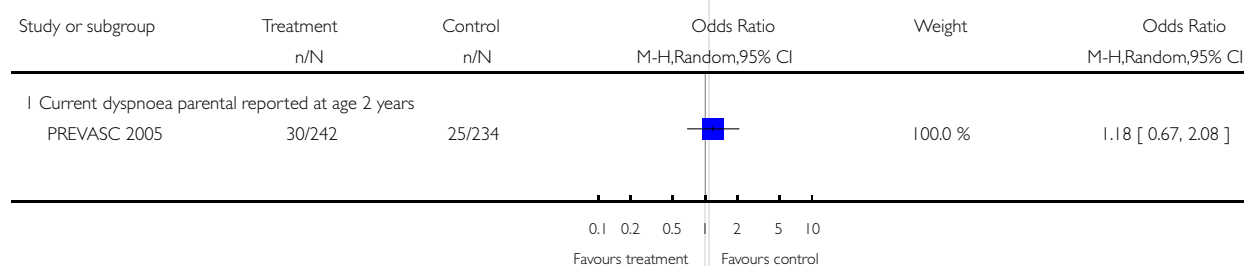


Analysis 4.1. Comparison 4 Current dyspnoea parental reported ITT, Outcome 1 Multifaceted.

Review: Mono and multifaceted inhalant and/or food allergen reduction interventions for preventing asthma in children at high risk of developing asthma

Comparison: 4 Current dyspnoea parental reported ITT

Outcome: 1 Multifaceted

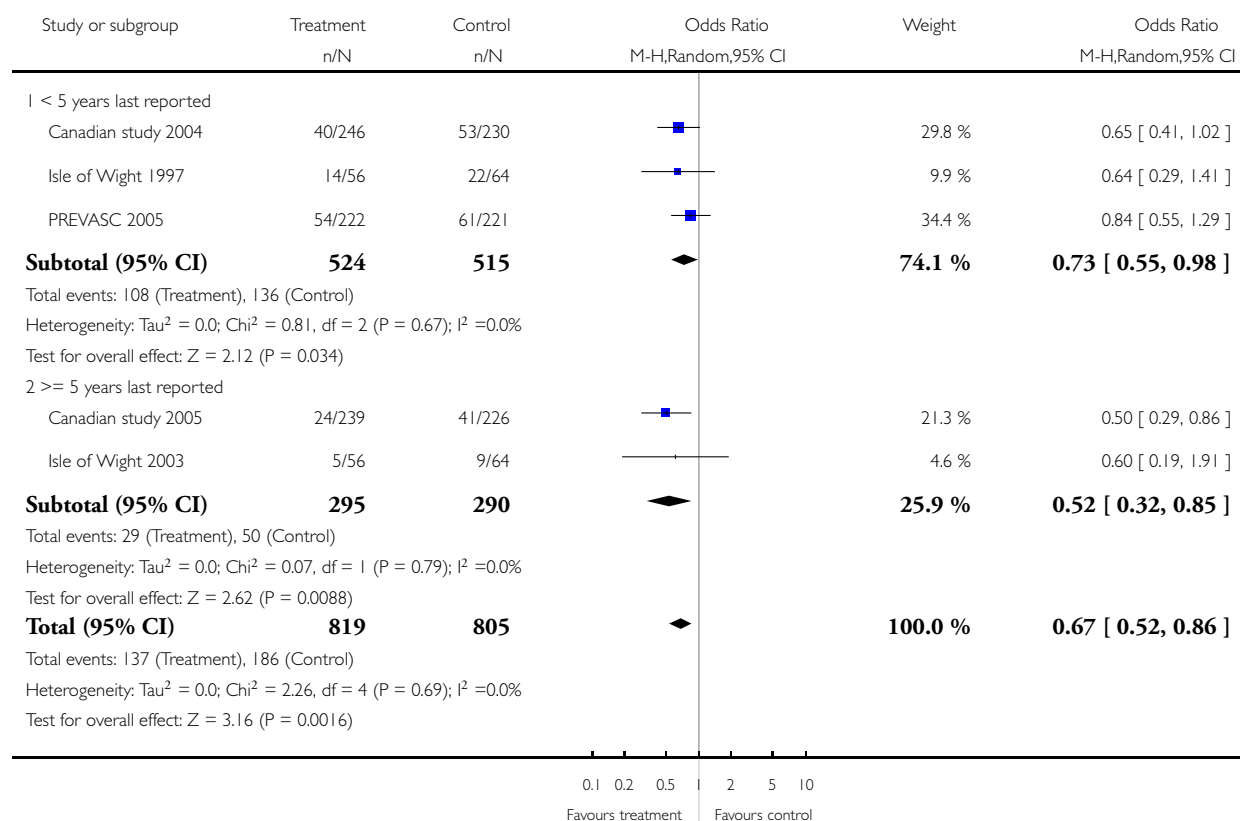


Analysis 5.1. Comparison 5 Sensitivity analyses current asthma on treatment, Outcome 1 Multifaceted interventions.

Review: Mono and multifaceted inhalant and/or food allergen reduction interventions for preventing asthma in children at high risk of developing asthma

Comparison: 5 Sensitivity analyses current asthma on treatment

Outcome: 1 Multifaceted interventions

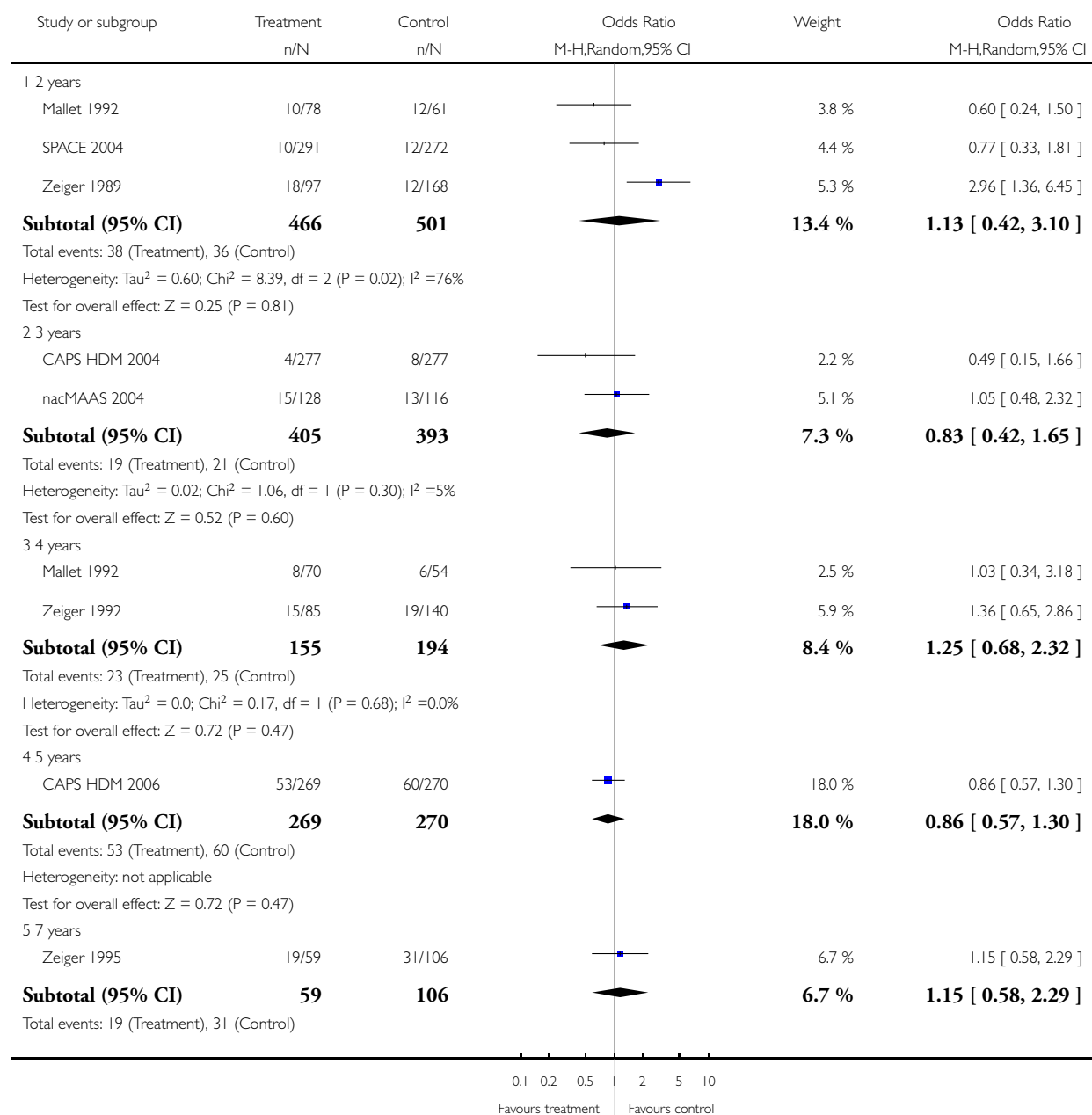


Analysis 5.2. Comparison 5 Sensitivity analyses current asthma on treatment, Outcome 2 Mono-faceted interventions.

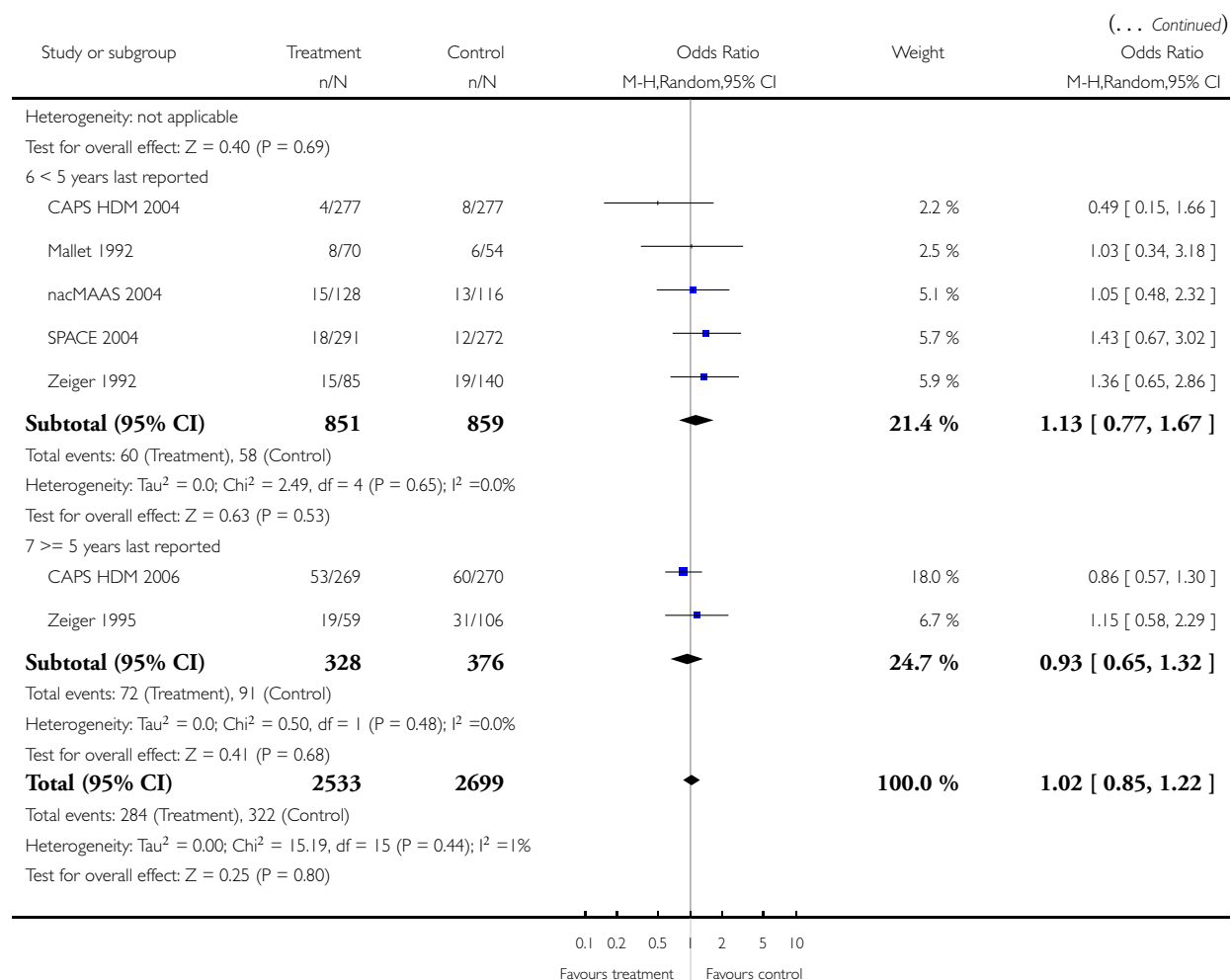
Review: Mono and multifaceted inhalant and/or food allergen reduction interventions for preventing asthma in children at high risk of developing asthma

Comparison: 5 Sensitivity analyses current asthma on treatment

Outcome: 2 Mono-faceted interventions



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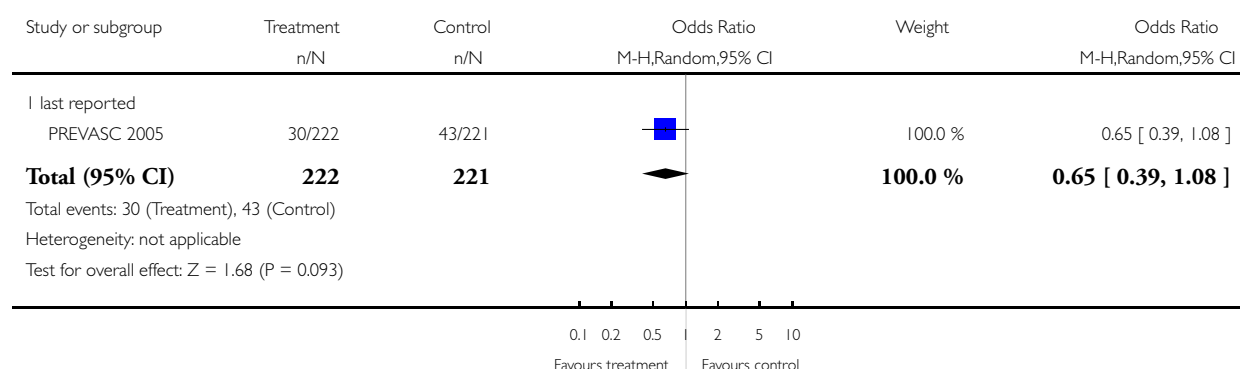


Analysis 6.1. Comparison 6 Sensitivity analyses current dyspnoea on treatment, Outcome 1 Multifaceted interventions.

Review: Mono and multifaceted inhalant and/or food allergen reduction interventions for preventing asthma in children at high risk of developing asthma

Comparison: 6 Sensitivity analyses current dyspnoea on treatment

Outcome: 1 Multifaceted interventions

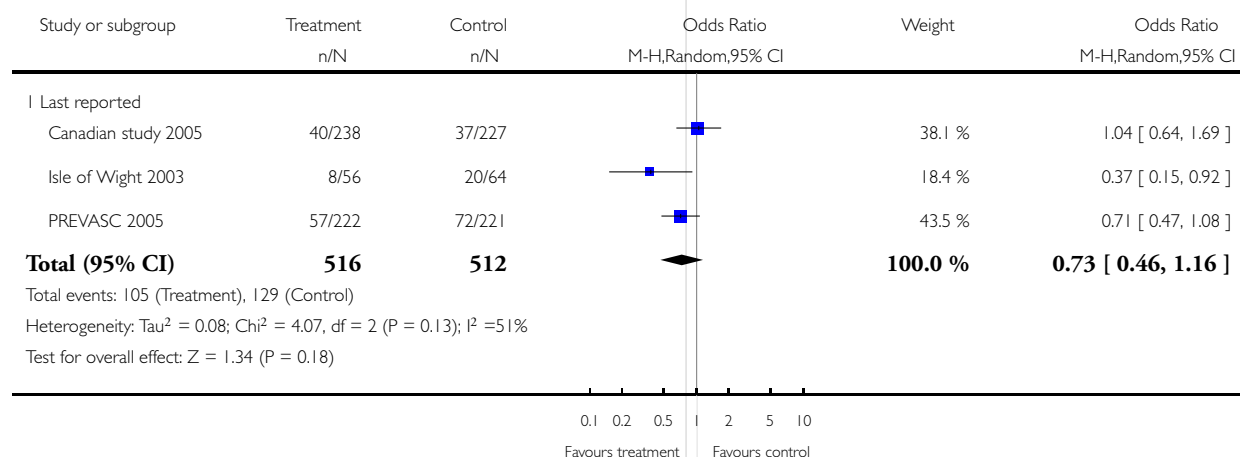


Analysis 7.1. Comparison 7 Sensitivity analyses current nocturnal cough on treatment, Outcome 1 Multifaceted interventions.

Review: Mono and multifaceted inhalant and/or food allergen reduction interventions for preventing asthma in children at high risk of developing asthma

Comparison: 7 Sensitivity analyses current nocturnal cough on treatment

Outcome: 1 Multifaceted interventions

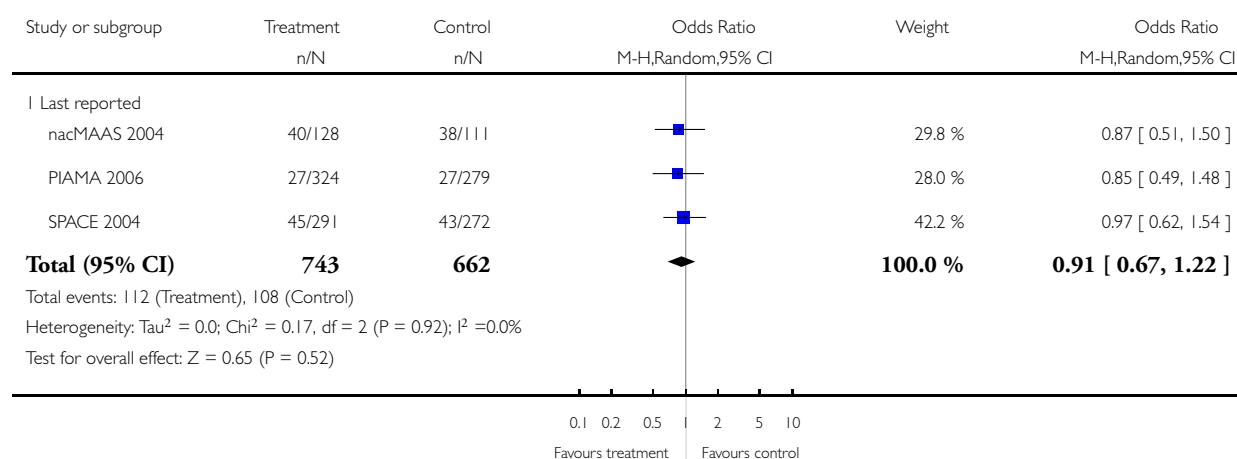


Analysis 7.2. Comparison 7 Sensitivity analyses current nocturnal cough on treatment, Outcome 2 Mono-faceted interventions.

Review: Mono and multifaceted inhalant and/or food allergen reduction interventions for preventing asthma in children at high risk of developing asthma

Comparison: 7 Sensitivity analyses current nocturnal cough on treatment

Outcome: 2 Mono-faceted interventions

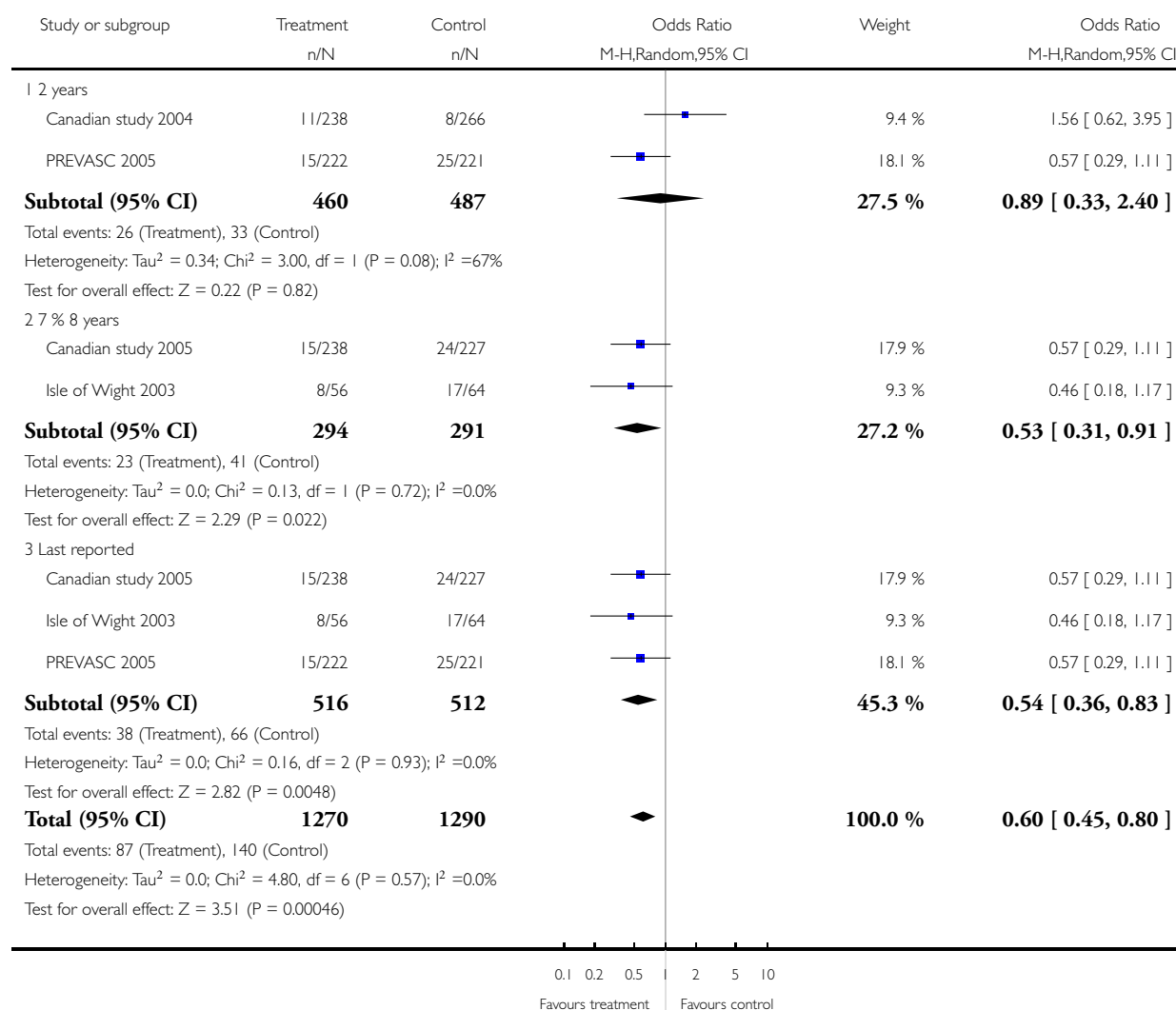


Analysis 8.1. Comparison 8 Sensitivity analyses current wheezing on treatment, Outcome 1 Multifaceted interventions.

Review: Mono and multifaceted inhalant and/or food allergen reduction interventions for preventing asthma in children at high risk of developing asthma

Comparison: 8 Sensitivity analyses current wheezing on treatment

Outcome: 1 Multifaceted interventions

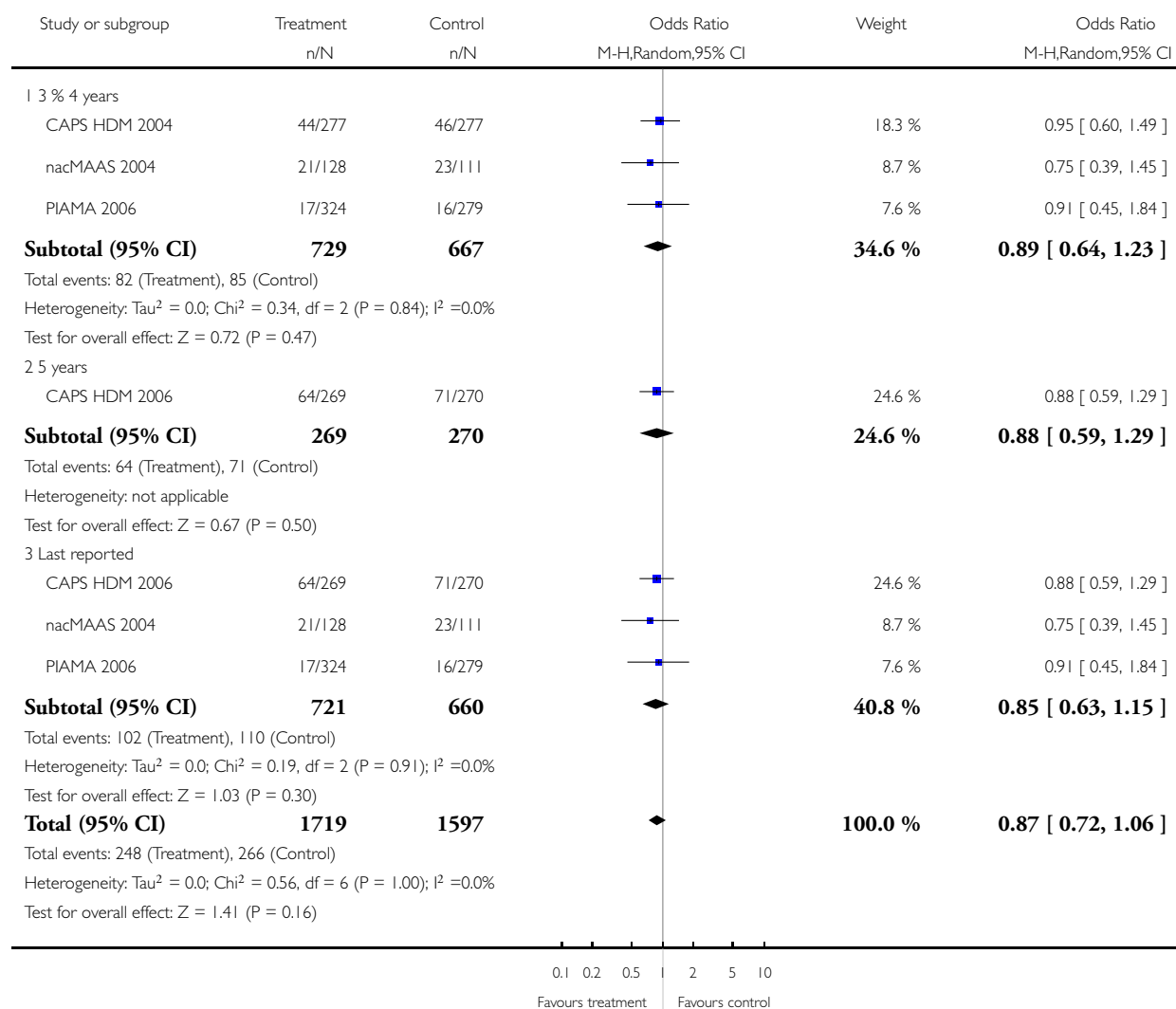


Analysis 8.2. Comparison 8 Sensitivity analyses current wheezing on treatment, Outcome 2 Mono-interventions.

Review: Mono and multifaceted inhalant and/or food allergen reduction interventions for preventing asthma in children at high risk of developing asthma

Comparison: 8 Sensitivity analyses current wheezing on treatment

Outcome: 2 Mono-interventions



HISTORY

Protocol first published: Issue 2, 2007

Review first published: Issue 3, 2009

22 October 2008	Amended	Converted to new review format.
14 October 2008	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

TM: Initiation of protocol; literature search; selection of eligible studies; quality assessment of studies; consultant regarding analyses; first author.

JK: Protocol development; consultant regarding RevMan use; comment on drafts; co-author.

AS: Comment on drafts; co-author.

AK: Protocol development; comment on drafts; co-author.

GW: Comment on drafts; co-author.

ED: Comment on drafts; co-author.

JM: Comment on drafts; co-author.

CPvS: Protocol development; consultant regarding inclusion, exclusion and analyses; quality assessment; comment on drafts; co-author.

DECLARATIONS OF INTEREST

The authors are associated with one of the studies included in the current review.

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Internal sources

- No sources of support supplied

External sources

- the Dutch Asthma Foundation, Netherlands.