

Allergen avoidance in the primary prevention of asthma

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Purpose of review

Six primary prevention studies trialing environmental modifications to reduce asthma in children have published results of clinical outcomes. All are still in progress.

Recent findings

In the Isle of Wight study, mite and food avoidance were evaluated to age 9 months. At 8 years, children in the active group had less current wheeze, wheeze with bronchial hyperresponsiveness and atopy ($P \leq 0.05$). The Canadian Primary Prevention Study examined avoidance of inhalant and food allergens. At 1 year there was a reduction in probable asthma and rhinitis in the active group. The Study on the Prevention of Allergy in Children in Europe tested avoidance of inhalant and food allergens. At 1 year there was less atopy and sensitization to mites in the active group. In the Childhood Asthma Prevention Study both mite avoidance and a dietary supplement of omega 3 fatty acids were analysed in a factorial design. At age 18 months, children in the dietary intervention group had significantly less wheeze. Eczema was more common amongst children using the mite avoidance measures. The Prevention and Incidence of Asthma and Mite Allergy Study is a placebo-controlled study of mite avoidance. At 2 years, there was a small reduction in nocturnal cough without a cold in the active group. The Manchester Asthma and Allergy Study included stringent environmental control. At 1 year prescribed medication for wheeze and wheeze with shortness of breath were significantly less common in the active group than the control group.

Summary

Although initial results look promising, further follow up of the ongoing cohorts is required before any recommendations can be made within the public health context.

Keywords

primary prevention, asthma, environmental control

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Abbreviations

aOR	adjusted odds ratio
CaPPS	Canadian Primary Prevention Study
CAPS	Childhood Asthma Prevention Study
MAAS	Manchester Asthma and Allergy Study
PIAMA	Prevention and Incidence of Asthma and Mite Allergy Study
SPACE	Study on the Prevention of Allergy in Children in Europe

Introduction

Avoiding allergens which cause symptoms in those who are sensitized seems logical. This strategy clearly works for seasonal rhinitis. Avoiding sensitizing agents in the workplace helps in occupational asthma and the sooner the avoidance begins the better. A set of measures can be used to reduce exposure to inhalant allergens in the home [1•]. Such measures may benefit children with asthma [2], but results of studies in adults have been disappointing [3•].

The strong association between allergic sensitization and childhood asthma raises the question of whether reducing exposure to allergens, from or even before birth, can reduce sensitization and whether this has any effect on the development of allergic disease. These 'primary prevention' studies are, by design, long term and will take many years to report any definitive findings.

In this review we will describe the studies in progress which have published results of clinical outcomes. Tables 1–4 compare the design, effectiveness of measures used and clinical outcomes reported. There are other studies in progress (including PREVASC – Prevention of Asthma in Children based in The Netherlands [4] and Childhood asthma prevention study in Southampton, UK) which have not yet reported on clinical outcomes and so have been excluded from this review. Most of the studies described also contain a large observational arm, but these findings are not reviewed here. The review will focus on studies of inhalant allergens rather than foods. As asthma is difficult to diagnose definitively in young children, most studies have reported on symptoms generally associated with asthma such as cough and wheeze. In addition, most have reported on allergic sensitization and eczema.

Isle of Wight study

This was the first study to implement an intervention designed to reduce exposure to inhalant allergens as part of a primary prevention programme [5–7,8••]. Entry criteria were two first-degree relatives with allergic disease (asthma, eczema or rhinitis) or one first-degree relative with allergic disease plus a cord blood IgE greater than 0.5 kU/l. A total of 120 children were included (58 active and 62 control) [5]. The protocol for the active group was one of combined avoidance of food and dust mite allergens to age 9 months. Acaricides were applied to carpets in the bedroom, living room and to upholstered furniture at birth, 3, 6 and 9 months, and

Table 1. Summary of allergen avoidance measures used in different studies

Features of study	MAAS	PIAMA	CAPS	CaPPS	SPACE	Isle of Wight
Selection of cases	Both parents atopic on skin testing to inhalant allergens	Mother allergic using questionnaire only	One first degree relative with current asthma	One first degree relative with asthma or two with IgE-mediated disease	One parent with asthma rhinitis or eczema and +ve skin test or specific IgE	Two or more immediate family members with asthma or eczema or rhinitis
Encasings to parental bed	Supplied and fitted to mattress, duvet and pillows before 16 weeks of pregnancy (Intervent)	Supplied, but mattress and pillow only, third trimester (not duvet) (allergy control products)	Only if child slept in parental bed	Supplied and fitted to mattress, duvet and pillows (Intervent)	Only if the child was likely to sleep in this bed, mattress only	No
Encasings to child's bed	Yes, custom made to fit cot and carrycot mattress, and later to bed (mattress, duvet and pillows)	Yes, standard size	Mattress was encased (Auspharm Pty Ltd)	Yes to mattress	Yes to mattress (unless the mattress was vinyl)	Infants in both groups slept on polyvinyl-covered mattresses with vented head area
Wash bedding > 55°C	Yes, weekly	Yes, regularly at > 60°C	Washed bedding in acaricidal detergent every 3 months	Yes, weekly/fortnightly	Yes, weekly for curtains, bedding, pillow and soft toys	No comment
Acaricide	Supplied for dust reservoirs with high mite allergen at baseline	No	Only as part of laundry instructions	To bedroom carpets and sofa before birth, at 4 months and at 8 months	No	Applied to living room and bedroom floor and upholstery, repeatedly to age 9 months
Smooth flooring in nursery	Yes, vinyl cushion floor supplied and fitted	No intervention to floor	No, but given washable play mat	Advised to remove all carpets, especially bedroom	Advised to remove carpet	No
Cat and dog owners	Excluded from this part of study	No comment	Cat owners excluded	Advised to part with furry pets, or failing this to keep them outside	Advised to part with pets or keep out of child's room	36% active, 38% control
Dietary intervention	None	None	Yes, but see text	Third trimester or lactating avoid nuts and fish. Partly hydrolysed formula supplied if not breastfed/after weaning. No cow's milk, seafood or peanuts in infancy	Introduction of solid food and soy after 6 months, hypoallergenic formula if not breastfed (except in UK), milk, eggs and fish after 12 months	If not breastfed given soya-based protein hydrolysate. No dairy, egg, wheat, nuts, fish or soya to age 9 months (same for lactating mothers).
Other	Supplied vacuum cleaner with HEPA filter and hot washable soft toy	None	Advised not to smoke	Smoking cessation encouraged or smoke outside	Ventilate bedroom, damp dust, store toys in cupboards	No
Control group	Nothing supplied	Cotton covers supplied, see text for second control group	No placebo covers supplied	Nothing supplied	No placebo covers	Nothing supplied

MAAS, Manchester Asthma and Allergy Study; PIAMA, Prevention and Incidence of Asthma and Mite Allergy Study; CAPS, Childhood Asthma Prevention Study; CaPPS, Canadian Primary Prevention Study; SPACE, Study on the Prevention of Allergy in Children in Europe; HEPA, High efficiency particulate air filter.

Table 2. Effectiveness of avoidance measures on mite allergen exposures, results reported for active group versus control group, median values, total allergen recovered, unless otherwise stated. No measurements taken in SPACE

Allergen levels before and after intervention	MAAS (Der p 1 in ng/m ²)	PIAMA (Der p 1 + Der f 1 in ng/m ²)	CAPS (Der p 1 µg/g)	CaPPS (Der p 1 + Der f 1 in µg/g) (taken from figures)	Isle of Wight
Der p 1 PM pre	325 versus 240	298 versus 414	NR	~ 1.4 versus ~ 1.8	NM
Der p 1 PM post	19 versus 569 (at 3 years) <i>P</i> <0.001	158 versus 309 (at 1 year) <i>P</i> <0.05	NR	~ 0.7 versus ~ 2 (at 2 years) <i>P</i> <0.001	NM
Significantly lower than control group					
Der p 1 CM at birth	1.25 versus 1.25	136 versus 114	3.27 versus 5.2	~ 2.8 versus ~ 1.2	No dust
Der p 1 CM post	49.5 versus 456 (at 3 years) <i>P</i> <0.001	190 versus 398 (at 1 year) <i>P</i> <0.05	6.12 versus 22.18 (at 18 months) <i>P</i> <0.001	~ 1 versus ~ 1 (at 2 years)	No dust
Significantly lower than control group					
Other	Fel d 1 and Can f 1 both significantly lower at age 3 years in CM and PM in active group			Not at 2 years, but transiently lower at 4 months Fel d 1 lower in active group PM in homes without a cat, no difference in homes with cats	Mean Der p 1 in LF, CF and S fell from 25.9 to 6 µg/g (at 9 months), <i>P</i> ≤0.05

SPACE, Study on the Prevention of Allergy in Children in Europe; MAAS, Manchester Asthma and Allergy Study; PIAMA, Prevention and Incidence of Asthma and Mite Allergy Study; CAPS, Childhood Asthma Prevention Study; CaPPS, Canadian Primary Prevention Study; PM, parental mattress; NR, not reported; NM, not measured; CM, child's mattress; LF, living room floor; CF, child's floor; S, sofa.

Table 3. Clinical outcome measures in allergen avoidance studies, results quoted are for active group (A) compared with control group (C)

	MAAS	PIAMA	CAPS	SPACE	CaPPS
Age of report	1 year	2 years	18 months	1 year	1 year
Sensitization to mite	2% (A), 1% (C), NS	IgE at 1 year, 0.7% (A), 0.8% (C), NS	~ 10% all groups	1.9% (A), 5% (C), <i>P</i> <0.03	0% (A), 0.4% (C)
Sensitization to cats	3% (A), 0% (C), NS	Not specifically reported	0–1% all groups	NR	3.7% (A), 1.6% (C)
Sensitization to food allergens	14% (A), 11% (C), NS (egg)	Not specifically reported	11–12.5% all groups	5% (A), 5% (C) (egg)	No difference, <i>P</i> =0.6
Atopy	17% (A), 14% (C), NS	14.4% (A), 14% (C), NS	18–21%, <i>P</i> =0.96	6% (A), 10.7% (C), <i>P</i> <0.03	4.6% (A), 4.4% (C), <i>P</i> =0.4
Wheeze	↓ Severe wheeze with SOB, or after exertion, ↓ medication for wheeze <i>P</i> ≤0.05	No difference	↓ In dietary intervention group only, <i>P</i> =0.02	No difference for 'wheezy bronchitis' 18.1% (A), 17.8% (C)	NR
Cough	No difference	↓ Night cough without cold	No difference	NR	NR
Asthma (see text for definition in each study)	Too young, NR	Too young, NR	No difference, but less oral steroid use in mite avoidance group, <i>P</i> =0.04	Too young	15.1% (A), 20.2% (C), <i>P</i> =0.04 for aOR
Eczema	40% (A), 37% (C), NS	↑ If no mite allergen in cot mattress, but no difference between groups at 1 year	↑ In mite avoidance group, <i>P</i> =0.03	11.6% (A), 13.5% (C)	NR

MAAS, Manchester Asthma and Allergy Study; PIAMA, Prevention and Incidence of Asthma and Mite Allergy Study; CAPS, Childhood Asthma Prevention Study; SPACE, Study on the Prevention of Allergy in Children in Europe; CaPPS, Canadian Primary Prevention Study; NS, not significant; NR, not reported; SOB, shortness of breath; aOR, adjusted odds ratio.

infants in both groups slept on polyvinyl-covered mattresses with vented head area [7]. Lactating mothers were asked to avoid dairy, eggs, wheat, fish, soya and nuts, and these foods were not introduced in the infant's diet until after 9 months of age [5]. Those infants not breastfed were given a soy-based hydrolysed formula. No placebo intervention was offered to the control group. Mite allergen levels were measured at birth and throughout the first year of life. Levels of Der p 1 fell significantly at 9 months (see Table 2) but after the

intervention, Der p 1 levels were still higher than the baseline levels seen in other studies [5]. At 9 months, however, levels in the active group were significantly lower than in the control group.

Published results on clinical follow up at age 1 [5], 2 [6], 4 [7] and 8 years [8••] are summarized in Table 4. Follow up of all 120 children was achieved at each time point. A reduction in sensitization and in wheeze was reported at age 1 year. At ages 2 and 4 years, differences in

Table 4. Results at different time points from the Isle of Wight study

	1 year	2 years	4 years	8 years (unadjusted <i>P</i> values)
Sensitization to mite	None (A), NR (C)	1.7% (A), 9.7% (C), <i>P</i> < 0.1	5.2% (A), 24.2% (C), <i>P</i> < 0.02	11% (A), 31% (C), <i>P</i> = 0.01
Sensitization to cats	1 (A), NR (C)	1.7% (A), 11.3% (C), <i>P</i> < 0.05	1.7% (A), 11.3% (C)	7.3% (A), 16.1% (C), <i>P</i> = 0.16
Sensitization to food allergens	1.7% (A), ~ 10% (C)	3.45% (A), 4.8% (C), (to egg) NS	4–5% (A), 6–11% (C), NS	0% (A), 8.1% (C), <i>P</i> = 0.06
Atopy	NR	5.2% (A), 25.8% (C) <i>P</i> < 0.005	13.8% (A), 33.9% (C), <i>P</i> < 0.02	20% (A), 46.8% (C), <i>P</i> = 0.003, on skin test
Current wheeze	NR	NR	NR	13.8% (A), 27.4% (C), <i>P</i> = 0.08
Nocturnal cough	NR	NR	NR	13.8% (A), 32.3% (C), <i>P</i> = 0.02
Study physician diagnosed asthma	7% (A), 19% (C)	15.5% (A), 27.4% (C), NS	24% (A), 35% (C) (wheeze/cough) NS	9.6% (A), 15.5% in (C), <i>P</i> = 0.4, (wheeze + BHR)
Bronchial responsiveness	ND	ND	ND	2.7 (A), 12.3 (C), <i>P</i> = 0.03 (DRR)
Eczema	7% (A), 19% (C)	13.8% (A), 24.2% (C), NS	13.8% (A), 24.2% (C), <i>P</i> < 0.05	NR
'Allergic disorder'	14% (A), 40% (C), <i>P</i> < 0.005	26% (A), 48% (C), <i>P</i> < 0.005	32.7% (A), 54.8% (C), <i>P</i> < 0.02	NR

A, active group; C, control group; NR, not reported; NS, not significant; BHR, bronchial hyperresponsiveness; DRR, dose response ratio; ND, not done.

respiratory symptoms between the groups failed to reach statistical significance. At age 8 years, sensitization to mite was reduced by more than 50% in the active group, despite modest reductions in mite allergen levels. In the multivariate analysis, the active group participants were significantly less likely to have current wheeze (adjusted odds ratio (aOR) 0.26, 95% CI 0.07–0.96, *P* = 0.04), nocturnal cough (aOR 0.22, 95% CI 0.06–0.83, *P* = 0.02), wheeze with bronchial hyperresponsiveness (aOR 0.11, 95% CI 0.01–1.02, *P* = 0.05) and atopy (aOR 0.21, 95% CI 0.07–0.62). Despite modest reductions in mite allergen levels, this combined intervention has resulted in statistically significant reductions in important clinical outcomes such as wheeze with bronchial hyperresponsiveness, which are all the more impressive given the small numbers in the study. It is impossible to determine, however, which part of the intervention programme is responsible for the effect.

Canadian Primary Prevention Study

In the Canadian Primary Prevention Study (CaPPS), children at high risk of allergic disease (see Table 1) were recruited antenatally, and 251 of the 278 randomized to the active group and 242/267 in the control group were available for follow up at 1 year. The intervention was multifaceted and included measures to reduce exposure to inhalant as well as food allergens (see Table 1). The clinical outcomes are reported at age 1 year [9], and the effectiveness of the intervention measures are reported at 2 years [10].

Compliance with mattress encasings was excellent and, as a result, mite allergens were significantly reduced in the parental bed throughout the study. For the child's mattress, levels were low in both groups after birth, and many dust samples too small to assay for allergen were

excluded from the analysis, which may explain why no difference in mite allergens was found between the active and control groups. Compliance with acaricides (applied by the study nurses) was also excellent, but this intervention was relatively ineffective. There was no reduction in the use of carpets, and there was a similar reluctance to part with the family pet. Fel d 1 levels in homes from which cats were removed gradually fell over the 2-year period, but there was no difference between study groups.

At age 1 year, the authors assigned the participants as having asthma (possible or probable) based on an a priori standard of frequency and duration of episodes of cough or wheeze, together with breathlessness and asthma medication usage. Another clinical outcome was rhinitis without colds. Using these descriptions, there was a significant reduction in probable asthma in the active group, as well as a reduction in rhinitis. Unfortunately, no data were presented on the relative frequencies of wheeze and cough in the two groups.

Study on the Prevention of Allergy in Children in Europe

The Study on the Prevention of Allergy in Children in Europe (SPACE) included newborn children from Austria, Germany and the UK [11]. Methods varied slightly between centres, but parents were generally screened antenatally and recruited if there was a history of allergic disease and evidence of sensitization on skin test or specific IgE in either parent. In total 696 children were included in the three centres. The intervention was multifaceted towards both inhalant and food allergens. Mite allergen avoidance focused on the infant's bed, the mattress of which was encased (unless it was vinyl). Other measures are outlined in Table 1. No measure-

ments of allergen levels in homes were undertaken. Mothers were advised to breastfeed children, and hypoallergenic formula was recommended as an alternative (except in the UK). Parents were also advised to delay the introduction of potentially allergenic foods. Compliance with the measures was reported to be good. Results reported at 1 year showed a reduction in sensitization to mites and also in atopy. There was no difference in the proportion of children who had ever wheezed (21% in both groups).

The Childhood Asthma Prevention Study

The Childhood Asthma Prevention Study (CAPS) was a multicentre parallel group randomized controlled trial which began in Sydney, Australia in 1997 [12]. Women were screened during pregnancy to identify unborn children with one first degree relative with current asthma. Those with cats were excluded and suitable women were randomized to one of four study groups: mite avoidance with placebo dietary intervention ($n=155$); mite avoidance with active dietary intervention ($n=153$); active dietary intervention alone, no mite avoidance ($n=159$); and placebo dietary intervention, no mite avoidance ($n=149$). No placebo measures were used for mite allergen avoidance and the active measures are described in Table 1. Although a statistically significant reduction in mite levels was seen when active measures were used [13], these levels were still higher than pre-intervention levels seen in other studies.

The dietary intervention was not designed to reduce exposure to potentially allergenic foods, but to increase dietary omega 3 fatty acids from age 6 months. For breastfed children this took the form of one 500 mg capsule of tuna fish oil to be taken daily from age 6 months. For children who were weaned before age 6 months, the parents were asked to add the supplement to the formula milk. Families were also supplied with canola-based oils and spreads which are rich in omega 3 fatty acids. Those not receiving the active intervention were given daily supplements of sunola oil and polyunsaturated oils and margarines.

Clinical outcomes at age 18 months were available on 554 children [14••]. Despite the fact that a significant proportion of children had become sensitized to inhalant and food allergens ($\sim 20\%$), there was no difference in rates of sensitization between the groups (Table 3). Almost 50% of the children had wheezed at some time during the first 18 months of life, and a similar percentage had had bronchodilator drugs prescribed. Those in the active dietary intervention group had significantly less wheeze than those on the placebo supplements (42.8% versus 52.6%, $P=0.02$), and most other wheeze indicators were lower in this group but did not all reach statistical significance. Eczema (both

reported and on inspection) was higher amongst those using the mite allergen avoidance measures, but the authors have suggested that this may be a sweat rash related to the surface of the cover used (E. Tovey, personal communication).

Prevention and Incidence of Asthma and Mite Allergy Study

The Prevention and Incidence of Asthma and Mite Allergy Study (PIAMA) is a cohort study of over 4000 children which began recruitment in 1996 in The Netherlands [15]. Within this cohort is an intervention study of 810 infants, selected because their mothers reported allergy on a questionnaire during pregnancy. The atopic status of the father was determined only after recruitment [16]. These study participants were randomly allocated to receive active mite proof encasings for the mattress and pillows of the parental and infant beds or cotton placebo encasings in a double-blind manner. No encasings were supplied for the duvet or blankets and advice was given to the active group to wash bedding regularly at more than 60°C (see Table 1) [17]. For the parental mattress, baseline levels of group 1 mite allergen were low in both groups, with a median value of less than 2 µg/g. One year after introduction of the intervention, levels were significantly lower in the active group compared with the control group, but there was little change in the absolute value of total allergen recovered (see Table 2). For the child's mattress, over the first year levels of mite allergen increased in both groups, but were significantly higher in the control compared with the active group. The actual difference in levels was small, however, with the active group approximately half that of the control group (Table 2). No change was made to the flooring, but over 40% of homes in the observational part of the study had smooth floors in the child's room [16], a situation very different to that seen in the UK. By age 2 years, exposure to pets (cats and dogs) approached 50% in both groups [16].

Outcome measures at age 2 years have recently been reported [18]. Although children in the active group were more likely to have had recurrent wheeze during the first year of life, in the regression analysis at 2 years, the only significant difference between groups was a reduction in night-time cough without a cold in the active group (aOR 0.65, 95% CI 0.4–1.0; Table 3). There was no difference in levels of serum total IgE or atopy at 1 year. The authors went on to investigate the effect of allergen exposure irrespective of group and reported statistically higher rates of atopic dermatitis amongst those exposed to no mite allergen in the mattress at 1 year. This result was apparently unchanged when stratified for group allocation, and no assessment was made of atopic dermatitis at age 2 years. There were no

significant associations between mite allergen exposure at age 3 months and wheezing at age 2 years. Follow up is planned to age 8 years to see how these interesting but preliminary observations develop [15].

Manchester Asthma and Allergy Study

The Manchester Asthma and Allergy Study (MAAS) is a whole population birth cohort study ($n \approx 1000$), with a nested intervention study in the high-risk group [19]. Participants were recruited from the antenatal clinic, where prospective parents were skin tested to inhalant allergen and answered a simple questionnaire regarding symptoms and diagnoses of allergic disease. Participants were allocated to a risk group before birth (high risk – both parents atopic, medium risk – one parent atopic, and low risk – neither parent atopic with no history of allergic disease). Pet (cat and dog) ownership was recorded at recruitment and those at high risk with no pets were randomly allocated to follow stringent environmental control (high risk active, $n=145$) or normal regime (high risk control, $n=146$). The environmental control regime included the fitting of mite proof encasings to the parental mattress, duvet and pillows by 16 weeks of pregnancy, advice to hot wash bedding weekly at over 55°C, supply of a high filtration vacuum cleaner and Acarosan to apply to dust reservoirs with high mite allergen levels. Just before the birth of the child, custom-made cot and carrycot mattresses (made of mite proof fabric) were supplied to the family, carpets were removed from the nursery and a vinyl cushion floor was fitted. A hot washable toy was also supplied. No attempt was made to introduce placebo devices into the control homes. The control group knew they were taking part in an allergen avoidance study and compliance with the regime was measured in the active group and use of allergen avoidance measures by the control group was recorded.

A significant and sustained reduction in exposure to mite, cat and dog allergens was shown in the homes of the children in the active group [20,21]. Clinical outcome measures on the effect of the environmental control were only published for age 1 year [21]. There was slightly more atopy in the high-risk active group compared with the control group (17% versus 14%), but this did not reach statistical significance ($P=0.5$). Asthma-like symptoms were consistently lower in the active group compared with the control group and this reached statistical significance for attacks of severe wheeze with shortness of breath, prescribed medication for wheezy attacks and wheeze after playing or exertion ($P<0.05$). No difference was seen for eczema between the groups. Assessment at intervals of 2–3 years is planned and further results will be published soon.

Conclusion

All studies have focused on children from atopic families. Only one of the six studies included placebo measures which allowed the study to be double blind (PIAMA), but this study incorporated the least stringent measures of environmental control. More stringent regimes make blinding impossible, at least for the investigators. Encasing the cot mattress is the only measure common to all studies, with advice on washing the second most common. Four of the studies included a dietary intervention, but only one was of factorial design which allowed the investigators to determine which of the interventions was responsible for the difference in clinical outcomes (CAPS).

The largest reductions in allergen levels were seen in MAAS. These reductions reflect the fact that this was by far the most stringent set of environmental control measures, and that pet owners were excluded from this part of the study. However, all five studies in which allergen levels were measured achieved some statistically significant reduction in levels, at the very least introducing a difference in exposures between groups.

Except for the Isle of Wight study, clinical outcomes have so far been reported at age 2 years or younger. Although these results are interesting, they are preliminary and are not going to change clinical practice. It is interesting to note that much higher rates of sensitization to mite are in Australia, irrespective of group. Rates of atopy are not so different between studies, except perhaps in CaPPS in which they tend to be lower. For studies reporting during the first 2 years of life, parentally reported wheeze was lower only in MAAS and in those children who received supplements of omega 3 fatty acids.

Ongoing prevention cohorts have provided us with a wealth of information, but much longer follow-up is required before we can be sure that the interventions do not cause any harm, and can confidently give any advice within the public health context.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

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