

*Original article***Prevention of asthma during the first 5 years of life: A randomized controlled trial**

Guy B. Marks, PhD,^{a,b,c} Seema Miharshahi, MPH,^d Andrew S. Kemp, PhD,^{b,d} Euan R. Tovey, PhD,^{a,b} Karen Webb, PhD,^b Catarina Almqvist, PhD,^{a,b,c} Rosario D. Ampon, MAppStat,^a Daniel Crisafulli, BSc,^{a,c} Elena G. Belousova, MSc(AppMath),^{a,c} Craig M. Mellis, MD,^{b,d} Jennifer K. Peat, PhD,^d and Stephen R. Leeder, PhD,^b
for the Childhood Asthma Prevention Study team Sydney, Australia

Background: Early life exposures may be important in the development of asthma and allergic disease.

Objective: To test house dust mite (HDM) avoidance and dietary fatty acid modification, implemented throughout the first 5 years of life, as interventions to prevent asthma and allergic disease.

Methods: We recruited newborns with a family history of asthma antenatally and randomized them, separately, to HDM avoidance or control and to dietary modification or control. At age 5 years, they were assessed for asthma and eczema and had skin prick tests for atopy.

Results: Of 616 children randomized, 516 (84%) were evaluated at age 5 years. The HDM avoidance intervention resulted in a 61% reduction in HDM allergen concentrations ($\mu\text{g/g}$ dust) in the child's bed but no difference in the prevalence of asthma, wheeze, or atopy ($P > .1$). The prevalence of eczema was higher in the active HDM avoidance group (26% vs 19%; $P = .06$). The ratio of ω -6 to ω -3 fatty acids in plasma was lower in the active diet group (5.8 vs 7.4; $P < .0001$). However, the prevalence of asthma, wheezing, eczema, or atopy did not differ between the diet groups ($P > .1$).

Conclusion: Further research is required to establish whether other interventions can be recommended for the prevention of asthma and allergic disease.

Clinical implications: House dust mite avoidance measures and dietary fatty acid modification, as implemented in this trial

during infancy and early childhood, did not prevent the onset of asthma, eczema, or atopy in high-risk children. (*J Allergy Clin Immunol* ■■■■;■■■:■■■-■■■.)

Key words: Allergen avoidance, ω -3 fatty acids, prevention, birth cohort, house dust mite

During the 1990s, there was widespread concern about the high and increasing burden of illness due to asthma, particularly among children.^{1,2} Evidence of substantial variation in prevalence rates between ethnically similar populations living in different geographical regions or cultural contexts^{3,4} strongly implied a role for lifestyle and environmental factors in the etiology and expression of asthma and allergic disease. Furthermore, long-term cohort studies revealed that asthma in childhood is an important risk factor for asthma in later life.⁵

Exposure to house dust mites (HDMs) and their allergens was 1 environmental factor postulated to have an important role in promoting asthma.⁶ Sensitization to HDM allergens was strongly linked to the presence of asthma, particularly in humid, coastal regions,⁷ and there was evidence that exposure to high levels of HDM increased the risk of developing asthma.^{8,9} Diet also varies substantially with lifestyle and cultural factors and may explain some of the variation in asthma prevalence. Cross-sectional studies in Australia during the 1990s found that children who regularly consumed oily fish, which contain high levels of ω -3 fatty acids, were less likely to have airway hyperresponsiveness and asthma.¹⁰ In addition, preschool children who regularly consumed oils and spreads containing polyunsaturated fats that have a higher proportion of ω -6 fatty acids had an increased risk of asthma-like symptoms compared with those not consuming these products.¹¹

We and others¹² concluded that the appropriate way to test the hypothesis that these exposures were, indeed, risk factors for asthma, and at the same time evaluate strategies relevant to the prevention of asthma at a population level, was to test them in a randomized controlled trial. Hence, we embarked on a trial to test the effect, in children with a family history of asthma, of interventions designed to reduce exposure to HDM allergens and, separately, to increase the ratio of ω -3 to ω -6 fatty acids in the diet,

From ^athe Woolcock Institute of Medical Research, ^bthe University of Sydney, ^cthe Cooperative Research Centre for Asthma, and ^dthe Children's Hospital at Westmead.

Supported by National Health and Medical Research Council of Australia, Cooperative Research Centre for Asthma, New South Wales Department of Health, Children's Hospital Westmead. Dr Almqvist was funded by the Swedish Heart Lung Foundation and Swedish Society of Medicine. Contributions of goods and services were made by Allergopharma Joachim Ganzer KG Germany, John Sands Australia, Hasbro, Toll Refrigerated, AstraZeneca Australia, and Nu-Mega Ingredients Pty Ltd. Goods were provided at reduced cost by Auspharm, Allersearch, and Goodman Fielder Foods.

Disclosure of potential conflict of interest: C. M. Mellis has consultant arrangements with Merck Sharp & Dohme, Altana Pharma. The rest of the authors have declared that they have no conflict of interest.

Received for publication November 30, 2005; revised April 3, 2006; accepted for publication April 4, 2006.

Reprint requests: Guy B. Marks, PhD, Woolcock Institute of Medical Research, PO Box M77, Missenden Road Post Office, New South Wales 2050, Australia. E-mail: g.marks@unsw.edu.au.

0091-6749/\$32.00

© 2006 American Academy of Allergy, Asthma and Immunology

doi:10.1016/j.jaci.2006.04.004

Abbreviation used

HDM: House dust mite

both implemented from birth to age 5 years, on the risk of asthma and allergic disease at age 5 years.

METHODS

The study design has been described in detail previously,¹³ and only key features are presented here. The study was a randomized, parallel-group controlled trial using a factorial design that separately tested 2 interventions.

The study was approved by the Human Research Ethics Committees of the University of Sydney, Children's Hospital Westmead, and Western and South Western Sydney Area Health Services.

Participants

Between September 1997 and November 1999, we recruited pregnant women whose unborn children were at increased risk of developing asthma because 1 or more parents or siblings had asthma or wheezing. We excluded those with a pet cat at home, strict vegetarians, women with a nonsingleton pregnancy, and infants born earlier than 36 weeks of gestation.¹³

We randomized participants, after signed consent was obtained at approximately 36 weeks of gestation, into active intervention or control groups for both HDM avoidance and dietary fatty acid modification using a procedure that we have described previously.¹³

There was a planned policy of withdrawing infants after randomization who had birth weights less than 2.5 kg, significant congenital malformations, or other significant neonatal disease.

Interventions

Details of the interventions are provided in the Online Repository for this article at www.jacionline.org.

The active HDM avoidance intervention used both physical and chemical methods to reduce exposure where the child was sleeping and playing, commencing before the birth of the child.¹³ Physical methods included the application of an allergen-impermeable barrier to the child's bed and pillow and regular washing of bedding. At 3-month intervals, parents added a benzyl benzoate-containing solution (final concentration 0.03%) to the wash. We provided parents in both the active and control HDM avoidance groups with advice about ensuring adequate ventilation, regular vacuuming, and avoidance of humidifiers or vaporizers.

The active diet intervention was intended to increase the proportion of ω -3 long-chain polyunsaturated fatty acids in the diet and reduce the content of ω -6 fatty acids.¹³ Parents were provided with oils and spreads for use with food preparation and food oil capsules to add once daily to the child's formula from the time the child started bottle-feeding, or to solid foods from age 6 months, whichever was earlier. For the active group, we provided canola-based oils and spreads, which are low in ω -6 fatty acids, and tuna oil capsules, which contain ω -3 fatty acids. For the diet control group, we provided polyunsaturated oils and spreads, containing 40% ω -6 fatty acids, and Sunola oil (Crisco-Meadow Lea Foods Inc, Sydney, Australia) capsules, which are low in ω -3 fatty acids.

Assessment of adherence to the interventions

In the active HDM avoidance group, at each home visit when we collected dust specimens, the study nurses assessed the presence of the study mattress cover on the child's bed and asked the parents to

confirm that they had washed the bedding with the benzyl benzoate-containing solution.

We assessed self-rated adherence to the use of study oils and spreads and the weight of returned food oil capsules as described in this article's Online Repository at www.jacionline.org. We measured plasma fatty acids at 18 months, 3 years, and 5 years as an objective measure of both adherence to the dietary regimen and its effect on blood levels of fatty acids.

Assessments

Assessments were performed at ages 18 months, 3 years, and 5 years. We have reported the outcomes at the first 2 assessments previously.^{14,15}

At age 5 years, parents were interviewed about symptoms and diagnoses relevant to asthma and allergic disease using a pro forma questionnaire. We based questions on symptoms of asthma, eczema, and rhinitis on those used in published questionnaires.^{16,17} Participants were examined for the presence of flexural eczema.

Spirometric lung function and respiratory system resistance were measured as described in this article's Online Repository at www.jacionline.org.

We measured atopy by using skin prick tests to the ingested allergens salmon, peanuts, cow's milk, egg white, egg yolk, and tuna, and the inhalant allergens *Dermatophagoides pteronyssinus* (HDM), cockroach, cat, *Alternaria alternata*, rye grass and a grass mix (Hollister-Stier, Spokane, Wash), as previously described.¹⁵ Glycerol and histamine phosphate (6 mg/mL) were used as negative and positive controls, respectively. Wheal sizes that were ≥ 2 mm and were also $>$ negative control were classified as positive.

Blood was collected for the measurement of serum total IgE. Plasma fatty acids were measured by gas chromatography.

Fine dust was collected from the child's bed by using a standard protocol¹⁸ at 4 weeks; 3, 6, 9, and 12 months; and then at 6-month intervals throughout the trial. The concentration of Der p 1 per gram of fine dust was measured as previously described.¹⁸

Primary outcome variable

We defined probable current asthma at the age of 5 years as parental report of any wheeze in the previous 12 months at age 5 years and either a parental report of diagnosed asthma at ages 18 months, 3 years, or 5 years or a $>12\%$ increase in FEV₁ after bronchodilator at age 5 years.

Secondary outcome variables

The pattern of wheeze at age 5 years was classified according to international guidelines.¹⁹ We classified participants who had episodes of wheeze lasting a week or more as having *frequent episodic wheeze* if the episodes occurred 3 or more times and more often than every 6 weeks over a 12-month period or as having *infrequent episodic wheeze* if the episodes occurred less frequently. All other participants with wheeze—that is, participants whose episodes only lasted less than 1 week—were classified as having *other wheeze*. The remaining participants had *no wheeze*.

Cough without cold was defined as parental report of cough lasting a week or more that was not associated with a cold.

Rhinitis was identified by parental report of sneezing or runny, itchy, or blocked nose.

Current eczema was defined as the presence of flexural eczema on inspection (by the assessment nurse) or by parental report of a history of itchy rash coming and going for a period of 3 months or more²⁰ together with a history of seeking medical care for eczema and/or using steroid or emollient creams in the last 12 months. Other measures of eczema are presented in this article's Online Repository at www.jacionline.org.

The time course of wheezing illness was defined as *transient early wheeze* if it was present at 18 months and 3 years but not at 5 years, *late onset wheeze* if it was absent at 18 months and 3 years but present at 5 years, *persistent* if it was present at 18 months and/or at 3 years and also present at 5 years, and *never* if it was absent at all 3 assessments.

Blinding

The approach to blinding participants and research staff is described in this article's Online Repository at www.jacionline.org.

Statistical methods

Data were acquired in a Microsoft Access database and exported for analysis in SAS System for Windows version 8.02 (SAS Institute, Cary, NC).

The analysis plan, which was finalized before accessing the data, and sample size calculations are described in this article's Online Repository at www.jacionline.org.

Because we could not measure the primary outcome, the presence of asthma at age 5 years, in any participants until after recruitment was completed, we undertook no interim analysis. However, we have reported previously the complete outcome data at ages 18 months and 3 years.^{14,15}

RESULTS

As previously reported,²¹ 7171 women were screened, of whom 2095 (29%) were eligible for the study, and 616 (29% of those eligible) were enrolled as participants. A survey of 200 eligible nonparticipants revealed that, compared with participants, a lower proportion of parents were tertiary-educated but the parents did not differ in age or proportion who were Australian-born, in full time employment, or primigravida.²¹

At age 5 years, outcome data were available for 516 (84%) of the 616 randomized participants. Most withdrawals (64) occurred before the 18-month follow-up (see this article's Fig E1 in the Online Repository at www.jacionline.org). There were a further 22 withdrawals between 18 months and 3 years, and 12 between 3 and 5 years. Another 2 participants did not attend for assessment at age 5 years. There was an even distribution of withdrawals among the groups. Reasons for withdrawal included parental decision (32), lost contact (53), unrelated medical problem in the child (11), and protocol violation (incorrectly selected for study, not eligible, 2).

Table E1 compares the baseline characteristics of the participants whom we followed up at age 5 years with participants who had withdrawn in each of the study groups. Women who had withdrawn their children from participation at age 5 years were younger than women who allowed their children to continue to participate ($P < .0001$), and those children who had been withdrawn were more likely to have older siblings ($P = .05$). Rates of withdrawal did not differ between active and control groups of the HDM or diet interventions ($P > .2$).

Among participants assessed at age 5 years, the active and control groups of the HDM and diet interventions did not differ in parental age, parental birth in Australia, parental education, parental history of asthma, maternal

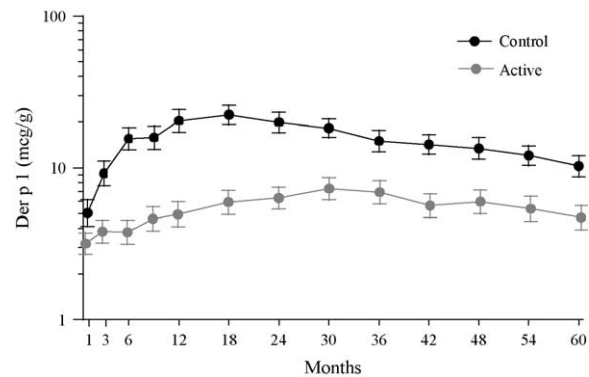


FIG 1. HDM allergen concentrations in fine dust collected from children's beds throughout the study period in the active and control HDM intervention groups. Geometric means and 95% CIs are shown.

history of smoking in pregnancy, or participant's sex (all P values $> .05$; see this article's Table E1 in the Online Repository at www.jacionline.org).

There was no significant interaction between the HDM avoidance intervention and the diet intervention in the effect on the study outcomes.

Adherence to the study interventions

We assessed the presence of the study mattress cover on the child's bed and use of the benzyl benzoate-containing solution for washing bedding on 13 occasions in the active HDM avoidance group. Covers were in place on 11 or more occasions in 53% of participants and on 8 or more occasions in 90% of participants. We confirmed the use of the benzyl benzoate-containing solution on 11 or more occasions in 71% of participants and on 8 or more occasions in 96% of participants.

The proportion of parents who reported that they remembered to use the study spreads and oils all of the time or most of the time during the study was 88%. This was the same in the active and control diet intervention groups ($P = .4$). However, median adherence to oil capsules during the period after age 2.5 years, estimated as the observed weight change of returned containers expressed as a percentage of the expected weight change, was only 56% (interquartile range, 26% to 80%) and was higher in the control diet group (median, 62%; interquartile range, 32% to 83%) than the active diet group (median, 51%; interquartile range, 16% to 78%; $P = .004$).

Effect of HDM avoidance intervention

The active HDM avoidance intervention achieved an average 61% reduction (95% CI, 57% to 65%) in the concentration of HDM allergen in dust collected from the child's bed over the period from 1 month to 5 years compared with the control group (Fig 1). At the 5-year follow-up, there was a 54% reduction in the active HDM intervention group.

Despite this reduction in HDM allergen levels in the child's bed, the intervention had no effect on the

TABLE I. Effect of HDM intervention on study outcomes*

Outcome	Prevalence or mean		Difference (95% CI)	Relative risk (95% CI)	P
	Control N = 260	Active N = 256	Active – control	Active/control	
Probable current asthma	60 23.1%	53 20.7%	–2.4% (–9.5% to 4.8%)	0.90 (0.65 to 1.24)	.6
Pattern of wheeze					.8
Frequent episodic	6 2.3%	3 1.7%			
Infrequent episodic	18 6.9%	22 8.6%			
Other wheeze	60 23.1%	56 21.9%			
No wheeze	176 67.7%	175 68.4%			
Time course of wheeze†					.6
Persistent	71 27.4%	64 25.0%			
Late onset	13 5.0%	17 6.6%			
Transient early	89 34.4%	84 32.8%			
Never	86 33.2%	91 35.6%			
Cough without colds	49 18.9%	42 16.4%	–2.4% (–9.0% to 4.1%)	0.87 (0.60 to 1.27)	.5
Rhinitis	103 39.6%	110 43.0%	3.4% (–5.1% to 11.9%)	1.08 (0.88 to 1.33)	.5
Current eczema‡	48 18.5%	65 25.7%	7.2% (0.0% to 14.3%)	1.39 (1.00 to 1.93)	.06
Skin prick tests	N = 250	N = 238			
Any atopy	117 46.8%	100 42.0%	–4.8% (–13.6% to 4.0%)	0.90 (0.74 to 1.10)	.3
Inhalant atopy	114 45.6%	94 39.5%	–6.1% (–14.9% to 2.7%)	0.87 (0.70 to 1.07)	.2
HDM atopy	91 36.4%	75 31.5%	–4.9% (–13.3% to 3.5%)	0.87 (0.67 to 1.11)	.3
IgE, IU/L	N = 201	N = 195		(Ratio of means)	
	81	65		0.80 (0.60 to 1.08)	.14
Baseline spirometry	N = 195	N = 186			
FEV ₁ , L	1.07	1.07	0.00 (–0.03 to 0.04)		.9
FEV ₁ /FVC ratio§	0.95	0.95			.6
Postbronchodilator spirometry	N = 194	N = 181			
FEV ₁ , L	1.10	1.11	0.01 (–0.03 to 0.04)		.8
FEV ₁ /FVC ratio§	0.96	0.96			.5
% change FEV ₁ §	3.4%	3.5%			.8
FOT baseline	N = 180	N = 185			
Rrs (cm H ₂ O/L/s)§	9.95	10.01			.8
FOT after bronchodilator	N = 177	N = 180			
Rrs (cm H ₂ O/L/s)§	8.66	8.55			.6
% Change Rrs§	–15.6%	–13.8%			.3

FOT, Forced oscillation technique; FVC, forced vital capacity; Rrs, resistance of the respiratory system.

*Values < 1 for relative risk and < 0 for differences favor the active intervention (except for FEV₁, for which positive values represent benefit for the intervention).

†No data for 1 control participant.

‡No data for 1 control and 3 active participants.

§Median values shown.

prevalence of asthma at age 5 years (Table I). Furthermore, there were no beneficial effects on the prevalence of any of the clinical or lung function outcomes measured at this age. There was a higher prevalence of

current eczema at age 5 years in the active HDM intervention group ($P = .06$). Four of 7 measures of eczema and its treatment showed worse outcomes in the active HDM avoidance group (see this article's Table E2 in the

Online Repository at www.jacionline.org). There was no reduction in the prevalence of sensitisation to HDM allergen. This finding was not different if a 3-mm threshold for a positive test was used.

Effect of dietary fatty acid modification

At ages 18 months, 3 years, and 5 years, the proportion of plasma fatty acids that were ω -3 was higher in the active diet group than in the control diet group, and the proportion that were ω -6 was higher in the control diet group than in the active diet group ($P < .0001$ for all comparisons; Fig 2). In the control diet group, the median ratios of ω -3 fatty acids to ω -6 fatty acids were 1:7.2, 1:7.7, and 1:7.4 at 18 months, 3 years, and 5 years, respectively, and in the active diet group, the median ratios were 1:4.9, 1:5.9, and 1:5.8, respectively.

The diet intervention did not have significant beneficial effects on any of the clinical, lung function, or allergic outcomes measured at age 5 years (Table II). In particular, there was no significant reduction in the prevalence of either asthma or eczema in the diet active intervention group compared with the diet control group.

Subgroup analyses

The effect of the HDM and diet interventions on clinical outcomes did not differ between participants with and without positive skin prick tests to any allergens at age 5 years ($P > .1$).

The effect of the interventions on risk of asthma and atopy at age 5 years did not differ between male and female subjects, between those with and without a maternal history of asthma, or between those with and without a paternal history of asthma (see this article's Table E3 in the Online Repository at www.jacionline.org).

DISCUSSION

We have shown that the implementation of feasible strategies directed at reducing exposure to HDM allergens and decreasing the ratio of ω -6 to ω -3 long-chain polyunsaturated fatty acids in the diet during the first 5 years of life does not reduce the prevalence of asthma, other wheezing illness, cough, rhinitis, eczema, or atopic sensitisation at age 5 years in children with a family history of asthma and wheezing. These negative results were obtained despite a 61% reduction in the concentration of HDM allergen in dust collected from the child's bed over the period of the study and a sustained alteration in the ratio of ω -3 to ω -6 fatty acids, respectively, attributable to the interventions.

Previous findings in this cohort

The lack of clinical benefit of both interventions at age 5 years is broadly consistent with the findings at earlier ages in this cohort. The HDM avoidance intervention was not associated with any reduction in adverse clinical outcomes at age 18 months or 3 years.^{14,15} There was a small reduction in the prevalence of HDM sensitisation

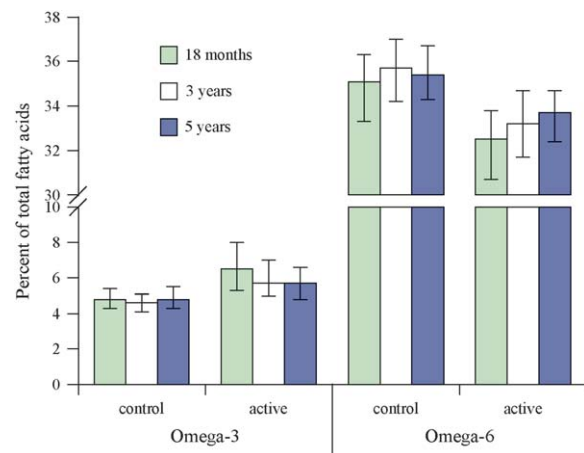


FIG 2. Proportion of ω -3 and ω -6 plasma fatty acids at ages 18 months, 3 years, and 5 years among participants followed up at 5 years. Medians and interquartile ranges are shown. All differences active vs control are significant, $P < .0001$.

at 3 years,¹⁴ but this did not persist to age 5 years. The dietary intervention was associated with a reduction in any wheeze, although not in wheeze without colds or any other clinical outcomes, at age 18 months,¹⁴ and reduction in cough associated with atopy at age 3 years.¹⁵ No beneficial effects on clinical outcomes were sustained to age 5 years.

Other evidence about environmental and dietary interventions, implemented from birth

In the mid to late 1990s, several randomized controlled trials in Europe and North America investigated the ability of interventions to prevent the onset of asthma and other allergic disease in high-risk children. Most of these trials implemented procedures to reduce exposure to HDM allergen during infancy, commencing at or before the birth of the child (Table III).²²⁻²⁶ The current study and 2 others^{24,26} tested the effect of HDM avoidance alone. All 3 achieved significant reductions in HDM allergens levels in household reservoirs. None of the 3 has demonstrated any beneficial effects on clinical outcomes at this stage. However, the other studies have reported outcomes only at ages 3 and 2 years, respectively. Other trials have incorporated food allergen avoidance,^{23,25} and 1 large Canadian trial²² implemented a multifaceted environmental intervention as well as food allergen avoidance. The Canadian study has shown clinically and statistically significant beneficial effects on outcomes at age 7 years. However, there was no effect on the prevalence of airway hyperresponsiveness, an objective marker of airway abnormality closely related to asthma.²⁷ The study in the Isle of Wight was much smaller and may have been underpowered. Nevertheless, there were strong trends toward beneficial effects at age 8 years in that trial,²³ and this is the only study in which the intervention resulted in a sustained reduction in the prevalence of atopy. It is not possible to draw definite conclusions about the effectiveness of specific avoidance interventions from the analysis of the

TABLE II. Effect of dietary fatty acid modification on study outcomes*

Outcome	Prevalence or mean		Difference (95% CI)	Relative risk (95% CI)	P
	Control N = 249	Active N = 267	Active – control	Active/control	
Probable current asthma	51 20.5%	62 23.2%	2.74% (–4.4% to 9.9%)	1.13 (0.82 to 1.57)	.5
Pattern of wheeze					.9
Frequent episodic	4 1.6%	5 1.9%			
Infrequent episodic	17 6.8%	23 8.6%			
Other wheeze	61 24.5%	55 20.6%			
No wheeze	167 67.1%	184 68.9%			
Time course of wheeze†					.3
Persistent	67 26.9%	68 25.6%			
Late onset	15 6.0%	15 5.6%			
Transient early	90 36.1%	83 31.2%			
Never	77 30.9%	100 37.6%			
Cough without colds	36 14.5%	55 20.6%	6.1% (–0.4% to 12.7%)	1.42 (0.97 to 2.09)	.09
Rhinitis	102 41.0%	111 41.6%	0.6% (–7.9% to 9.1%)	1.01 (0.83 to 1.25)	.9
Current eczema‡	59 24.0%	54 20.3%	–3.7% (–10.9% to 3.5%)	0.85 (0.61 to 1.17)	.4
Skin prick tests	N = 234	N = 254			
Any atopy	108 46.2%	109 42.9%	–3.2% (–12.1% to 5.6%)	0.93 (0.76 to 1.13)	.5
Inhalant atopy	102 43.6%	106 41.7%	–1.9% (–10.6% to 6.9%)	0.96 (0.78 to 1.18)	.7
HDM atopy	78 33.3%	88 34.7%	1.3% (–7.1% to 9.7%)	1.04 (0.81 to 1.33)	.8
IgE, IU/L	N = 193 79	N = 203 68		(Ratio of means) 0.86 (0.64 to 1.16)	.3
Baseline spirometry	N = 188	N = 193			
FEV ₁ , L	1.07	1.07	0.0 (–0.03 to 0.03)		.9
FEV ₁ /FVC ratio§	0.95	0.95			.8
Postbronchodilator spirometry	N = 185	N = 190			
FEV ₁ , L	1.10	1.11	0.00 (–0.03 to 0.04)		.9
FEV ₁ /FVC ratio§	0.95	0.96			.3
% change FEV ₁ §	3.17%	3.52%			.9
FOT baseline	N = 178	N = 187			
Rrs (cm H ₂ O/L/s)§	10.21	9.87			.3
FOT after bronchodilator	N = 175	N = 182			
Rrs (cm H ₂ O/L/s)§	8.80	8.47			.08
% Change Rrs§	–14.5%	–15.7%			.5

FOT, Forced oscillation technique; FVC, forced vital capacity; Rrs, resistance of the respiratory system.

*Values < 1 for relative risk and < 0 for differences favour the active intervention (except for FEV₁, for which positive values represent benefit for the intervention).

†No data for 1 active participant.

‡No data for 3 control participants and 1 active participant.

§Median values shown.

current published data, because there are important differences in the local environments in which the trials were conducted. In addition, the interventions and the outcomes measured vary among the trials. Nevertheless, it appears that HDM avoidance as a sole intervention does not

have beneficial effects on the onset and course of asthma and allergic disease in early life.

The current trial is the first in which an alteration in the balance of ω -3 and ω -6 long-chain polyunsaturated fatty acids in the diet has been implemented from birth, with a

TABLE III. Findings of clinical trials of HDM avoidance interventions, implemented from birth, for the prevention of asthma in children*

Study population	Intervention	Assessment age	Clinical outcomes	Atopic sensitization	Reference
First degree relative with asthma or wheeze, no household cat, Sydney Australia	HDM allergen avoidance, first 5 y of life	5 y	No effect on asthma, wheeze, cough or rhinitis; increase in eczema (RR, 1.39)	No effect (any positive SPT)	Current study
First-degree relatives with asthma or allergic disease, Vancouver and Winnipeg, Canada	Avoidance of HDM, pets, environmental tobacco smoke, day care, and cow's milk; first year of life	7 y	Reduced doctor-diagnosed asthma (RR, 0.44), wheeze (RR, 0.42); no effect on rhinitis, eczema, or AHR	No effect (any positive SPT)	Chan-Yeung et al ²²
First-degree relatives with allergic disease, Isle of Wight, UK	Food and HDM allergen avoidance; first 9 mo of life	8 y	Reduced nocturnal cough (RR, 0.43); nonsignificant trends to reduced wheeze (RR, 0.50) and reduced AHR (RR, 0.76)	Reduced atopy (any positive SPT; RR, 0.43)	Arshad et al ²³
Both parents atopic, no household pets, Manchester, UK	HDM allergen avoidance implemented from prenatal period	3 y	No effect on wheeze, cough, rhinitis, or eczema	Increased atopy (any positive SPT; RR, 1.61)	Woodcock et al ²⁴
First-degree relatives with allergic disease, Vienna (Austria), Isle of Wight (UK), Freiburg (Germany)	Food and HDM allergen avoidance, implemented from birth	2 y	No effect of asthma, wheeze, rhinitis, or eczema	No effect on HDM sensitization (SPT)	Horak et al ²⁵
Mother with allergic disease, The Netherlands	HDM allergen avoidance, implemented from prenatal period	2 y	No effect on wheeze, cough, rhinitis, or eczema	No effect on HDM sensitization (specific IgE)	Koopman et al ²⁶

AHR, Airway hyperresponsiveness; RR, relative risk; SPT, skin prick test; UK, United Kingdom.

*Only studies reporting clinical outcomes at age 2 y or older are included. The latest data from each study are cited.

view to reducing the incidence of asthma or allergic disease. Recently, another study has shown that fish oil supplementation of the diet of mothers with allergy during pregnancy resulted in attenuated cytokine responses to allergen by cord blood lymphocytes.²⁸ We do not know whether this earlier intervention results in sustained clinical benefits in later childhood.

Possible reasons for failure to show a clinical benefit

The most direct interpretation of the negative finding in this study is that the hypotheses are not supported, despite the observational data that led to their formulation. In relation to the HDM avoidance intervention, this conclusion is probably valid, because earlier results of this trial and other trials were also negative. However, it is also possible that, although we achieved substantial reductions in HDM allergen exposure, those reductions were not large enough to have biological consequences. Mean levels in the active HDM avoidance group were around 6 to 7 $\mu\text{g/g}$ for most of the study period, which is high by international

standards and a level at which observational studies suggest sensitization is likely.²⁹ Substantially lower levels were observed in intervention studies conducted in Europe. In the Prevention and Incidence of Asthma and Mite Allergy study, the median concentration of HDM allergen in dust collected from the child's mattress at age 12 months was 0.9 $\mu\text{g/g}$ in the active treatment group and 1.5 $\mu\text{g/g}$ in the placebo group.³⁰ In the Manchester study, the corresponding geometric mean concentrations of HDM allergen were approximately 0.2 $\mu\text{g/g}$ in the active treatment group and 1.0 $\mu\text{g/g}$ in the placebo group.³¹ Furthermore, reductions in reservoir levels only approximately reflect the reduction in personal exposure to HDM allergen because this measure is only moderately correlated with airborne sampling.^{32,33} There are no existing data that allow us to establish whether a larger reduction in HDM allergen would have resulted in effective prevention of asthma and, if so, how large that reduction would have to have been. However, 2 international studies that did achieve much lower levels of HDM allergen in the intervention group did not achieve clinical benefits.^{24,26}

The failure to detect an effect of the dietary intervention might be attributable to suboptimal adherence to and/or implementation of the intervention. Although parents reported that they were using the oils and spreads that were provided, weighing of returned containers indicated only moderate adherence to the expected use of the additive food oil capsules, and the ratio of ω -3 to ω -6 fatty acids in plasma in the active diet group decreased slightly between the ages of 18 months and 3 years. However, differences in plasma levels of ω -3 and ω -6 fatty acids between active and control groups were demonstrated throughout the 5-year study period, and the relative magnitude of the differences was similar to that observed in neonatal red cell membranes in a study that suggested that such changes, induced by maternal fish oil supplementation, might reduce neonatal lymphocyte allergen responsiveness.²⁸

It is also possible that the occurrence of asthma in the high-risk group we have selected, with a family history of asthma, is largely genetically determined, and that the population in whom environmental interventions are most likely to be effective are those without these genetic risk factors. In common with other investigators, we excluded these subjects from our study population and hence had no capacity to test that hypothesis.

Loss to follow-up may cause biased results in clinical trials. However, in this study, only 16% of the originally randomized cohort were not available for assessment at age 5 years. Hence, for the main study outcomes, important selection bias is unlikely. Participation rates for spirometry and measurement of total serum IgE were lower (see this article's [Table E1](#) in the Online Repository at www.jacionline.org) because of subjects being tested at home rather than at the testing center or, in some cases, technical difficulty with the procedures. It seems unlikely that this reason for nonparticipation would have led to serious selection bias.

Finally, it is possible that failure to show a clinical benefit results from lack of power. The study was designed (powered) to detect a 15% absolute reduction in the prevalence of asthma.¹³ Examination of the 95% CIs shows that we have excluded, with 95% confidence, a reduction in the prevalence of probable current asthma of 9.5% or greater for the diet intervention and 4.4% or greater for the HDM avoidance intervention. Hence, we met the power targets we had set. We have also excluded reduction in the prevalence of atopy of 12.1% or greater for the diet intervention and 13.6% or greater for the HDM avoidance intervention. We believe we have excluded a benefit of sufficient magnitude to warrant widespread implementation.

Increase in eczema in the active HDM avoidance group

At age 5 years, several measures of eczema and its treatment were worse in the active HDM avoidance group. However, the fact that there was no increase in the prevalence of visible eczema or seeking medical care for eczema at the time of the 5-year examination suggests that the observed excess skin disease was relatively mild.

There are several possible explanations for the increase in eczema in the HDM avoidance group, although none adequately explains the observations. It is possible that the HDM avoidance intervention, in addition to removing HDM allergen, also removed other, protective factors such as endotoxin in the local environment and that this resulted in an increase in eczema in the active intervention group.³⁴ This was 1 mechanism proposed for the increase prevalence of sensitization in the Manchester HDM avoidance trial.²⁴ However, in this study, there was no increase in the prevalence of atopy in the active HDM avoidance group. Another possible explanation is that higher mite allergen in the control group may have induced some form of immunologic tolerance, resulting in relatively less eczema in the control compared with the intervention group. However, the lack of any difference in the prevalence of HDM sensitization also makes this unlikely. Components of the HDM avoidance intervention may have contributed to the increased prevalence of eczema. Although it is feasible the encasings themselves may directly exacerbate eczema, this effect has not been observed in other intervention studies with encasings. It is also unlikely that the laundry additive contributed to the increase in eczema. The active ingredient, benzyl benzoate, was used in the wash at a concentration of 0.03%, and the residual concentration would be expected to be extremely low after subsequent rinsing and drying of bedding. Benzyl benzoate is routinely applied directly to the skin at concentrations of 5% in the treatment of scabies, and confirmed skin reactions linked to this treatment are rare.³⁵

CONCLUSION

The institution of HDM avoidance measures and dietary fatty acid modification, as implemented in this trial, in infancy and early childhood to prevent the onset of asthma and allergic disease in children at increased risk of asthma cannot be recommended. Indeed, the former may be contraindicated because of an increased risk of eczema. The positive findings from some other intervention trials and the observed temporal and geographic variation in the prevalence of asthma support the view that, under certain circumstances, asthma can be prevented. However, the most effective, practical forms of early life environmental modification and the circumstances under which it will be appropriate to implement them remain to be established.

We acknowledge the assistance of the Childhood Asthma Prevention Study research team. Research nurses included Nicola Vukasin, Craig Wainwright, Samantha Forbes, William Krause, Anne Tattam, and Kitty Ng. Stella Davis and Sally Criss assisted with processing blood specimens. We are especially grateful to the parents of the study subjects, whose commitment to the study over several years enabled us to complete our work.

REFERENCES

1. Burney P, Chinn S, Rona R. Has the prevalence of asthma increased in children? evidence from the national study of health and growth 1973-86. *BMJ* 1990;300:1306-10.

2. Peat JK, van den Berg RH, Green WF, Mellis CM, Leeder SR, Woolcock AJ. Changing prevalence of asthma in Australian children. *BMJ* 1994;308:1591-6.
3. Waite DA, Eyles EF, Tonkin SL, O'Donnell TV. Asthma prevalence in Tokelauan children in two environments. *Clin Allergy* 1980;10:71-5.
4. von Mutius E, Martinez F, Fritzsch C, Nicolai T, Roell G, Thiemann HH. Prevalence of asthma and atopy in two areas of West and East Germany. *Am J Respir Crit Care Med* 1994;149:358-64.
5. Jenkins M, Hopper J, Bowes G, Carlin J, Flander L, Giles G. Factors in childhood as predictors of asthma in adult life. *BMJ* 1994;309:90-3.
6. Platts-Mills T, de Weck A. Dust mite allergens and asthma: a worldwide problem. *J Allergy Clin Immunol* 1989;83:416-27.
7. Peat J, Woolcock A. Sensitivity to common allergens: relation to respiratory symptoms and bronchial hyper-responsiveness in children from three different climatic areas of Australia. *Clin Exp Allergy* 1991;21:573-81.
8. Korsgaard J. Mite asthma and residency: a case-control study on the impact of exposure to house-dust mites in dwellings. *Am Rev Respir Dis* 1983;128:231-5.
9. Sporik R, Holgate S, Platts-Mills T, Cogswell J. Exposure to house-dust mite allergen (*Der p 1*) and the development of asthma in childhood: a prospective study. *N Engl J Med* 1990;323:502-7.
10. Hodge L, Salome C, Peat J, Haby M, Xuan W, Woolcock A. Consumption of oily fish and childhood asthma risk. *Med J Aust* 1996;164:137-40.
11. Haby M, Peat J, Marks G, Woolcock A, Leeder S. Asthma in pre-school children: prevalence and risk factors. *Thorax* 2001;56:589-95.
12. Platts-Mills T, Vervollet D, Thomas W, Aalberse R, Chapman M. Indoor allergens and asthma. Third International Workshop, Cuenca. Spain. *J Allergy Clin Immunol* 1997;100:S1-24.
13. Mihrshahi S, Peat J, Webb K, Tovey E, Marks G, Mellis C, et al. The Childhood Asthma Prevention Study (CAPS): design and research protocol of a large randomised trial of the primary prevention of asthma. *Control Clin Trials* 2001;22:333-54.
14. Mihrshahi S, Peat J, Marks G, Mellis C, Tovey E, Webb K, et al. Eighteen-month outcomes of house dust mite avoidance and dietary fatty acid modification in the childhood asthma prevention study (CAPS). *J Allergy Clin Immunol* 2003;111:162-8.
15. Peat JK, Mihrshahi S, Kemp AS, Marks GB, Tovey ER, Webb K, et al. Three year outcomes of dietary fatty acid modification and house dust mite reduction in the Childhood Asthma Prevention Study (CAPS). *J Allergy Clin Immunol* 2004;114:807-13.
16. International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. Worldwide variation in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. *Lancet* 1998;351:1225-32.
17. Williams H, Robertson C, Stewart A, Ait-Khaled N, Anabwani G, Anderson R, et al. Worldwide variations in the prevalence of symptoms of atopic eczema in the international study of asthma and allergies in childhood. *J Allergy Clin Immunol* 1999;103:125-38.
18. Mihrshahi S, Marks GB, Criss S, Tovey ER, Vanlaar CH, Peat JK. Effectiveness of an intervention to reduce house dust mite allergen levels in children's beds. *Allergy* 2003;58:784-9.
19. Warner J, Nasipz C, Cropp G. Third international pediatric consensus statement on the management of childhood asthma. *Pediatr Pulmonol* 1998;25:1-17.
20. Williams H, Burney P, Hay R, Archer C, Shipley M, Hunter J, et al. The U.K. Working Party's diagnostic criteria for atopic dermatitis, I: derivation of a minimum set of discriminators for atopic dermatitis. *Br J Dermatol* 1994;131:383-96.
21. Mihrshahi S, Vukasin N, Forbes S, Wainwright C, Krause W, Ampon R, et al. Are you busy for the next five years? recruitment in the Childhood Asthma Prevention Study (CAPS). *Respirology* 2002;7:147-51.
22. Chan-Yeung M, Ferguson A, Watson W, Dimich-Ward H, Rousseau R, Lilley M, et al. The Canadian Childhood Asthma Primary Prevention Study: outcomes at 7 years of age. *J Allergy Clin Immunol* 2005;116:49-55.
23. Arshad SH, Bateman B, Matthews SM. Primary prevention of asthma and atopy during childhood by allergen avoidance in infancy: a randomised controlled study. *Thorax* 2003;58:489-93.
24. Woodcock A, Lowe LA, Murray CS, Simpson BM, Papis SD, Kissen P, et al. Early life environmental control: effect on symptoms, sensitization, and lung function at age 3 years. *Am J Respir Crit Care Med* 2004;170:433-9.
25. Horak F, Matthews S, Ihorst G, Arshad SH, Frischer T, Kuehr J, et al. Effect of mite-impermeable mattress encasings and an educational package on the development of allergies in a multinational randomized, controlled birth-cohort study - 24 months results of the Study of Prevention of Allergy in Children in Europe. *Clin Exp Allergy* 2004;34:1220-5.
26. Koopman LP, van Strien RT, Kerkhof M, Wijga A, Smit HA, de Jongste JC, et al. Placebo-controlled trial of house dust mite-impermeable mattress covers: effect on symptoms in early childhood. *Am J Respir Crit Care Med* 2002;166:307-13.
27. Toelle BG, Peat JK, Salome CM, Mellis CM, Woolcock AJ. Toward a definition of asthma for epidemiology. *Am Rev Respir Dis* 1992;146:633-7.
28. Dunstan JA, Mori TA, Barden A, Beilin LJ, Taylor AL, Holt PG, et al. Fish oil supplementation in pregnancy modifies neonatal allergen-specific immune responses and clinical outcomes in infants at high risk of atopy: a randomized, controlled trial. *J Allergy Clin Immunol* 2003;112:1178-84.
29. Wahn U, Lau S, Bergmann R, Kulig M, Forster J, Bergmann K, et al. Indoor allergen exposure is a risk factor for sensitization during the first three years of life. *J Allergy Clin Immunol* 1997;99:763-9.
30. van Strien RT, Koopman LP, Kerkhof M, Oldenwening M, de Jongste JC, Gerritsen J, et al. Mattress encasings and mite allergen levels in the Prevention and Incidence of Asthma and Mite Allergy study. *Clin Exp Allergy* 2003;33:490-5.
31. Custovic A, Simpson B, Simpson A, Hallam C, Craven M, Brutsche M, et al. Manchester Asthma and Allergy Study: low allergen environment can be achieved and maintained during pregnancy and early life. *J Allergy Clin Immunol* 2000;105:252-8.
32. Tovey ER, Mitakakis TZ, Sercombe JK, Vanlaar CH, Marks GB. Four methods of sampling for dust mite allergen: differences in "dust. *Allergy* 2003;58:790-4.
33. Tovey ER, O'Meara T, Marks G. Bed covers and dust mites [letter]. *N Engl J Med* 2003;349:1668-71.
34. Gehring U, Bolte G, Borte M, Bischof W, Fahlbusch B, Wichmann HE, et al. Exposure to endotoxin decreases the risk of atopic eczema in infancy: a cohort study. *J Allergy Clin Immunol* 2001;108:847-54.
35. Meneghini CL, Vena GA, Angelini G. Contact dermatitis to scabicides. *Contact Dermatitis* 1982;8:285-6.