

Letter to the Editor

Eight-year outcomes of the Childhood Asthma Prevention Study

To the Editor:

The Childhood Asthma Prevention Study is a randomized controlled trial to test the effectiveness of house dust mite (HDM) avoidance and dietary fatty acid modification during the first 5 years of life as strategies for the primary prevention of asthma and allergy in high-risk children. We have previously shown that although the interventions were successful in reducing HDM allergen concentration in dust collected from beds and increasing the ratio of ω -3 to ω -6 fatty acids in plasma at age 5 years, this was not accompanied by any effect on the prevalence of asthma, wheeze, or atopy at this age.¹

The aim of this study was to determine whether the interventions during the first 5 years of life reduced the prevalence of asthma, atopy, and/or related disorders at age 8 years. A secondary aim was to test whether the effect of the HDM avoidance intervention on asthma and related disorders was modified by the presence or absence of atopy.

The study design has been described previously.² The study was a randomized, parallel-group controlled trial using a factorial design that separately tested 2 interventions: HDM avoidance and dietary fatty acid modification (see Fig E1 and the Methods section in this article's Online Repository at www.jacionline.org). The interventions were implemented from birth to age 5 years. Results of assessments performed at ages 18 months, 3 years, and 5 years have been reported previously.^{1,3,4} The study was approved by the Human Research Ethics Committees of the University of Sydney, Children's Hospital at Westmead, and Sydney South West Area Health Services.

At age 8 years, we collected data on parental reports of their child's symptoms and treatment by means of interviewer-administered questionnaire. We also measured lung function by means of spirometry, airway hyperresponsiveness by means of a methacholine inhalation challenge test, allergic sensitization by means of a skin prick test, airway inflammation based on exhaled nitric oxide levels, and total and specific IgE levels and plasma fatty acids by means of blood tests. We also collected bed dust to

measure Der p 1 concentrations. Further details about these methods can be found in the Methods section of this article's Online Repository.

Poor asthma control was defined as 1 or more of the following in the preceding 12 months: more than 12 attacks of wheezing, disturbed sleep caused by wheezing at least once per week, wheezing limiting the child's speech to only 1 or 2 words at a time between breaths, use of a bronchodilator for nighttime waking or early morning chest tightness more than 3 times per week, or hospital emergency department visits or admissions for asthma.

At the 8-year assessment, outcome data were available for 450 (73%) of the original randomized 616 participant children. Between the 5- and 8-year assessments, 24 children withdrew from the study, and another 44 children were not available for testing at the time of the 8-year assessment.

Three years after cessation of the interventions, there was no longer any difference between the randomization groups in HDM allergen concentrations in the bed or plasma fatty acid levels. The mean Der p 1 concentrations in bed dust were 5.8 μ g/g (95% CI, 4.8-7.1) for the active group and 6.9 μ g/g (95% CI, 5.7-8.4) for the control group ($P = .2$). The median ω -3 to ω -6 fatty acids in plasma ratio was 1:6.9 (interquartile range, 1:8.1 to 1:6.1) for the active group and 1:7.3 (interquartile range, 1:8.4 to 1:6.1) for the control group ($P = .3$).

The prevalence of all clinical outcomes at age 8 years did not differ between the active and control groups of the HDM avoidance or the dietary modification interventions (Table I), except that there was a higher prevalence of wheeze among children in the active dietary modification group compared with those in the diet control group. There were no significant interactions between the 2 interventions ($P > .20$ for all outcomes).

The effect of the HDM avoidance intervention on the prevalence of poor asthma control differed between participants who were atopic and those who were not atopic. Among children who were atopic at 8 years of age, the active HDM avoidance intervention was associated with an absolute risk reduction of 10.6% (95% CI, 0.1% to 21.0%) in poor asthma control compared with those in the control group. In contrast, among those who were not atopic at this age, the active HDM avoidance

TABLE I. Effect of the interventions on clinical outcomes assessed at 8 years of age

Outcome	HDM intervention			Diet intervention		
	Active (%)	Control (%)	Absolute risk reduction* (95% CI)	Active (%)	Control (%)	Absolute risk reduction* (95% CI)
Atopy	43.9	46.1	2.2 (−7.5 to 12.0)	45.1	45.0	−0.2 (−9.9 to 9.6)
HDM allergy	33.2	37.9	4.7 (−4.6 to 14.1)	38.2	32.8	−5.4 (−14.8 to 3.9)
Wheeze	29.6	25.7	−3.9 (−12.2 to 4.4)	31.7	23.2	−8.6 (−16.8 to −0.4)
AHR	18.5	18.4	0.1 (−8.1 to 8.0)	18.0	19.0	1.0 (−7.1 to 9.0)
Asthma	23.2	21.7	−1.4 (−9.2 to 6.3)	24.8	20.0	−4.8 (−12.5 to 2.9)
Poor asthma control	8.6	10.9	2.2 (−3.2 to 7.7)	10.4	9.1	−1.3 (−6.8 to 4.1)
Eczema	14.4	15.0	0.6 (−6.1 to 7.3)	15.3	14.2	−1.1 (−7.8 to 5.6)
Rhinitis	32.3	27.8	−4.5 (−12.9 to 4.0)	30.4	29.6	−0.9 (−9.4 to 7.6)
Serum total IgE >1000 IU	9.7	8.6	−1.1 (−7.5 to 5.3)	8.5	9.9	1.5 (−4.9 to 7.8)
Specific anti-HDM IgE positive	43.0	42.4	−0.7 (−11.3 to 9.9)	44.8	40.4	−4.5 (−15.0 to 6.1)
FeNO >15 ppb	12.2	11.9	−0.3 (−6.7 to 6.1)	13.4	10.8	−2.6 (−9.0 to 3.8)

AHR, Airway hyperresponsiveness; FeNO, fraction of exhaled nitric oxide.

*Absolute risk reduction = control-active.

intervention was associated with an absolute risk reduction for poor asthma control of -5.5% (95% CI, -11.4% to 0.5% ; $P = .01$ for the difference in effect between atopic and nonatopic subjects). This significant effect on poor asthma control was also shown for the subgroup of atopic children with HDM atopy alone. Similar differences in the effect of the HDM intervention on poor asthma control at age 8 years were observed when subjects were classified according to atopic status at ages 18 months, 3 years, and 5 years, although the difference between atopic and nonatopic subjects was only statistically significant for atopy measured at 3 and 8 years of age. Atopic status did not significantly modify the effect of the HDM avoidance intervention on any of the other outcomes.

The finding that the HDM intervention was effective in reducing the risk of poor asthma control among atopic, but not nonatopic, participants might be important. Poor asthma control, which was defined with reference to the definition of asthma control used in current asthma guidelines,⁵ is responsible for most of the costs and consequences of this disease.⁶ The magnitude of the observed effect of the HDM avoidance intervention on poorly controlled asthma corresponds to a number needed to treat of 9.4 among atopic children. This compares well with other interventions for asthma. Furthermore, the HDM avoidance intervention we implemented was a simple and relatively inexpensive set of activities that were incorporated into the usual routine of the families. They were designed to be feasible for large-scale intervention and proved to be so. Hence although the HDM intervention did not prevent asthma, it did have a clinically important beneficial effect in an at-risk subgroup of the population.

This study shows that in children with a family history of asthma, neither HDM avoidance nor dietary fatty acid modification, as implemented in this study from birth to age 5 years, reduced the prevalence of asthma, atopy, or other atopic disorders at age 8 years. However, the HDM avoidance intervention did lead to a significant reduction in the prevalence of poorly controlled asthma among atopic children, but not among nonatopic children, at this age.

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METHODS

The study design has been described previously,^{E1} and aspects relevant to the 8-year follow-up 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 at Westmead, and Sydney South West Area Health Services.

Participants

Between September 1997 and November 1999, we recruited pregnant women whose unborn children were at increased risk of 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' gestation.^{E1}

Interventions

The interventions were implemented from birth to age 5 years. 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.^{E1} 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, 320 ng/L) 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 and reduce the content of ω -6 fatty acids.^{E1} 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.

Further details of the interventions are provided in the [Online Repository](http://www.jacionline.org) for our previous article^{E2} at www.jacionline.org.

Assessment of adherence to the interventions

Adherence to the interventions during the first 5 years of the randomized controlled trial has been reported previously.^{E2-E4} To determine whether there was any long-term effect of the intervention, at 8 years, we measured the concentration of the HDM allergen Der p 1 in a sample of dust that was collected from the child's bed, according to the protocol previously described.^{E5} Additionally, we measured plasma proportions of ω -3 and ω -6 fatty acids at this age.

Assessments

Assessments were performed at ages 18 months and 3, 5, and 8 years. We have reported the outcomes at the first 3 assessments previously.^{E2,E6,E7}

Symptom and diagnosis. Parents were interviewed about their child's symptoms and diagnoses relevant to asthma and allergic disease by using a *pro forma* questionnaire that was similar to that used at previous assessments. Participants were examined by trained research staff for the presence of flexural eczema.

Lung function. Subjects were requested to avoid using long-acting β -agonists for 12 hours and short-acting β -agonists for 6 hours before the test. Spirometric lung function was measured with the child standing without wearing a nose clip in accordance with American Thoracic Society recommendations,^{E8} except that a 6-second expiratory time criterion was not applied. The technician first explained and then demonstrated the procedure. The child performed the spirometric maneuver, and then the technician corrected any errors in technique. The child repeated the procedure until at least 3 acceptable flow-volume loops had been recorded. If the difference

between the best 2 acceptable values of FEV₁ was greater than 100 mL, the child was asked to repeat the maneuver to reduce the difference in FEV₁ to within 100 mL. The highest values for FEV₁ and forced vital capacity were selected from among the acceptable flow-volume loops. The spirometer used was a Spirocard (QRS Diagnostics, LLC, Plymouth, Minn), which was connected to a notebook computer running SpiroScore+ V.2.6 spirometry software (Bird Healthcare, Melbourne, Australia).

Airway hyperresponsiveness was measured at the 8-year hospital-based clinical assessment in subjects whose baseline FEV₁ was greater than 70% of predicted value. A methacholine inhalation challenge test was performed according to the rapid method.^{E9} Normal saline (the control solution) and methacholine solutions were administered by using handheld nebulizers (De Vilbiss No 45). FEV₁ was measured by means of spirometry 60 seconds after each dose was administered. If the FEV₁ was greater than 100 mL less than the previous FEV₁, the test was repeated until 2 values within 100 mL were recorded. The highest of these reproducible values was selected by the technician for analysis. Repeated spirometric measurements were performed until either the final dose of methacholine had been administered or the FEV₁ had decreased to 20% or more below the postsaline value. Bronchoconstriction was reversed with albuterol.

A bronchodilator test was conducted on a separate day at the home visit. Spirometric values were measured as described above before and 10 minutes after the administration of 200 μ g of albuterol through a large-volume spacer. The percentage change in FEV₁ after 10 minutes was recorded.

Atopy. We measured atopy by using skin prick tests to the ingested allergens salmon, peanuts, 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.^{E7} Glycerol and histamine phosphate, 10 mg/mL, were used as negative and positive controls, respectively. Wheal sizes were measured 10 minutes later, and those that were greater than 3 mm and also greater than those elicited by the negative control were classified as positive.

Fraction of exhaled nitric oxide. Exhaled nitric oxide was measured at age 8 years by using the offline technique.^{E10} The test was performed with the subject breathing room air in through a scrubber that was designed to remove nitric oxide from ambient air. The subject was standing, had a nose clip on, and inhaled and exhaled 5 times through the scrubber, and then immediately after the fifth inhalation, the subject exhaled through a rotameter. The rotameter incorporated a flow sensor, and the subject was instructed to maintain the expiratory flow rate at about 200 mL/s by keeping a floating ball between 2 sets of flow rate markers. The device also incorporated a manually operated valve. Initially, the valve was set to be open to the room, allowing the technician to discard the dead-space volume. After approximately 1 to 2 seconds of expiration, the technician turned the valve to direct the airflow into a 3-L impermeable polyethylene (Scholle Industries, Adelaide, Australia) collecting bag. The subject was instructed to continue to exhale to near-residual volume. This procedure was repeated up to 2 or 3 times until approximately 1 L was collected in the bag.

Within 24 hours of collection (usually on the same day), the contents of the impermeable polyethylene bag were aspirated into a chemiluminescent analyzer (Model 42C; Thermo Environmental Instruments, Franklin, Mass) to measure the nitric oxide concentration in parts per billion.

Blood tests. Blood was collected for the measurement of serum total and HDM-specific IgE levels by means of immunoassay with the Pharmacia ImmunoCAP 250 system (Pharmacia CAP System; Pharmacia Diagnostics AB, Uppsala, Sweden). Plasma fatty acids were measured by means of gas chromatography.

HDM allergen concentration. Fine dust was collected from the child's bed at the 8-year assessment by using the same standardized vacuum protocol used while the HDM intervention was still in place. The concentration of Der p 1 per gram of fine dust was measured, as previously described.^{E11}

Primary outcome variable

We defined *asthma at age 8 years* as wheeze in the last 12 months at that age plus either ever-diagnosed asthma (reported at ages 18 months and 3, 5 or 8 years) or airway hyperresponsiveness (at 8 years).

Secondary outcome variables

Atopy was defined as a mean skin wheal diameter of greater than 3 mm and also greater than that elicited by the negative control for any inhaled or ingested allergen. At the 3-year and 18-month assessments, a 2-mm cutoff was used instead of the 3-mm cutoff.

HDM allergy was defined as a mean skin wheal of greater than 3 mm and also greater than that elicited by the negative control for HDM allergen.

Wheeze was defined as any wheeze in the last 12 months.

Airway hyperresponsiveness was defined as a $PD_{20}FEV_1$ (methacholine) value of less than 6.1 μ mol or greater than 12% bronchodilator response in children who did not have a methacholine challenge.

We defined *poor asthma control*^{E12} as being present in those participants with asthma who, in the preceding 12 months, had 1 or more of the following: (1) more than 12 attacks of wheezing, (2) disturbed sleep caused by wheezing 1 night per week or more often, (3) episodes of wheezing severe enough to limit the child's speech to only 1 or 2 words at a time between breaths, (4) need to use a bronchodilator for nighttime waking or early morning chest tightness more often than 3 times per week, or (5) visits to a hospital's emergency department or admissions to the hospital for asthma.

Rhinitis was defined as sneezing, rhinorrhea, or blocked nose without cold in the last 12 months.

Eczema was defined as flexural rash at the time of physical assessment or a history of recurrent itchy rash and use of topical treatments in the last 12 months.

Blinding

All assessments undertaken at the 8-year assessment were completed by staff who were blind to the child's original group allocation.

Statistical methods

All data were double entered, verified, and stored in a Microsoft Access 2003 database and analyzed in SAS 9.1 software (SAS Institute, Inc, Cary, NC).

Absolute risk reductions were calculated as the prevalence of outcomes in subjects in the control group minus the prevalence in subjects in the active intervention group. Ninety-five percent CIs were calculated for these

differences. Interactions were tested by using the Breslow-Day test for heterogeneity. *P* values of less than .05 were considered statistically significant.

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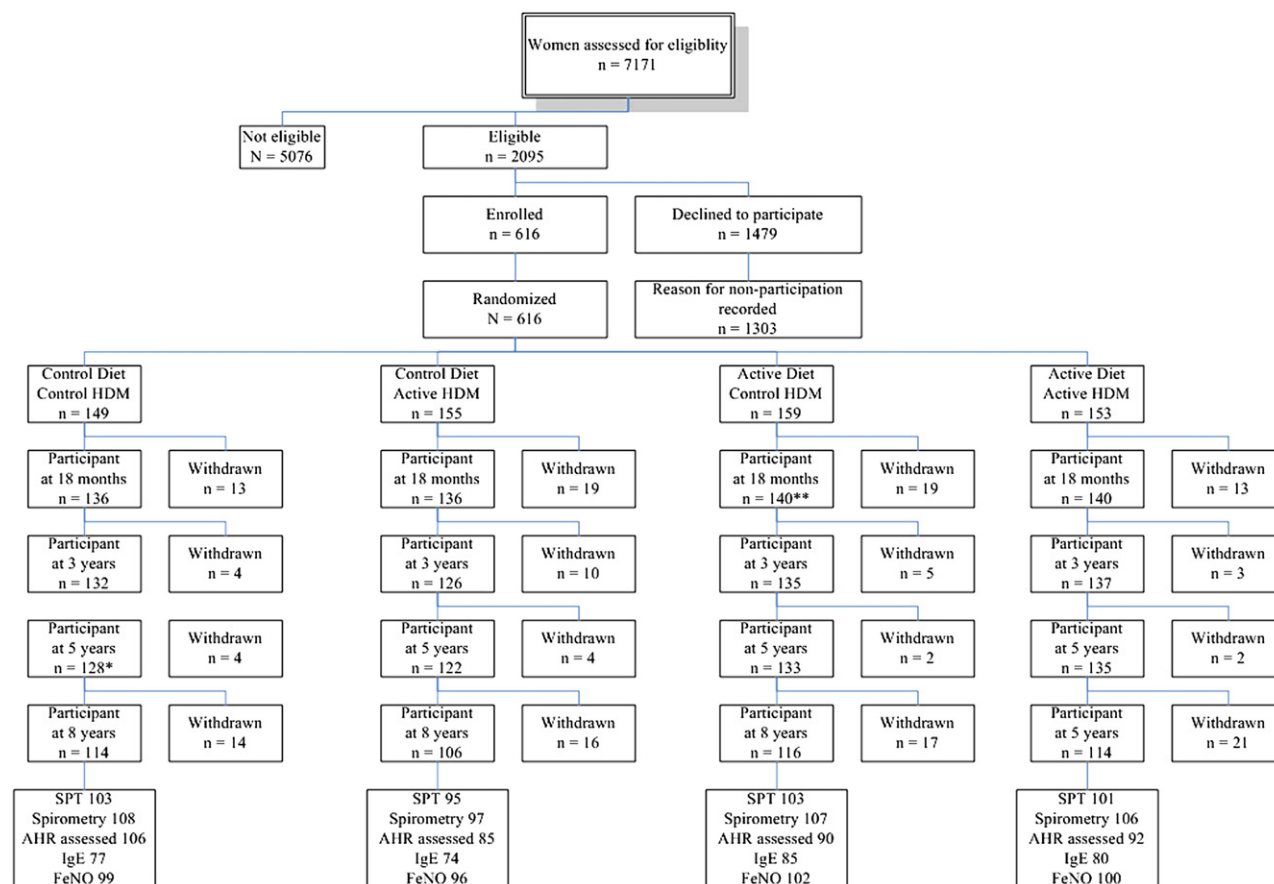


FIG E1. Flowchart for the Childhood Asthma Prevention Study (patients followed to age 8 years). *Two participants in the “Active Diet, Control HDM” group did not attend the 18-month assessment. **One participant in the “Control Diet, Control HDM” group and 1 participant in the “Active Diet, Active HDM” group did not attend the 5-year assessment. *AHR*, Airway hyperresponsiveness; *FeNO*, fraction of exhaled nitric oxide; *SPT*, skin prick test.