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VENTION

AND INTER-

VENTION OF

ATOPIC

DISEASE

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Due to the rapidly increasing prevalence of atopic disease worldwide, there is great interest in allergy prevention. The fact that exposure to high levels of allergens early in life appears to increase the risk for sensitization and allergic manifestations later in life has prompted studies of the possible effects of allergy prevention. Prevention efforts could be made at different stages of atopic development as defined below:

Primary prevention: Prevention or delay of immunological sensitization (i.e. appearance of IgE) and symptoms.

Secondary prevention: Prevention of the development of allergic disease, following sensitization and symptoms.

Tertiary prevention: Treatment of allergic diseases to reduce short-or long-term morbidity.

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PRIMARY PREVENTION

BY DIET

Several studies have examined the effects of primary prevention, notably by restricting the mother's diet during pregnancy and/or lactation, as well as the baby's intake during infancy.

The first controlled study to prevent atopy by allergen avoidance dates back to 1936 when Grulee and Sanford showed that eczema in infancy was reduced almost 7-fold in nearly 20,000 infants fed breast-milk rather than cow's milk (1).

The effect of a diet free from egg, cow's milk and fish for mothers during the first 3 months of lactation was evaluated in 65 children with a family history of atopy in Sweden (2). In the control group of 50 children, also with a family history of atopy, the mothers had a normal diet. Only non-smoking families without pets were considered. At the age of 4 years the cumulative prevalence of atopic dermatitis was significantly lower in the group where the mothers had adhered to a hypoallergenic diet during lactation whereas all other allergic manifestations were similar (Table 1).

The very long-term effect of breast-feeding was reported by a group in Finland who evaluated the occurrence of atopic manifestations in healthy newborns throughout childhood and adolescence until the age of 17 years (3). Breast-feeding was encouraged as long as possible and preferable for at least 6 months. Solid foods were started at 3.5 months of age according to a strict protocol. As shown in Figure 1 the prevalence of atopy was highest in the short-period breast-feeding group. The prevalence of eczema at ages 1 and 3 years was lowest in the prolonged breast-feeding group and respiratory allergy was most prevalent in the short or no breast-feeding group at ages 5, 10 and 17 years (Fig. 2). This study suggests that breast-feeding is prophylactic against atopic diseases throughout childhood and adolescence and particularly in children with substantial allergy.

In a prospective, California-based, controlled study of food allergen avoidance in infancy, the prophylactic-treated group included

TABLE 1

Cumulative Incidences (Cum Inc) and Current Prevalences (Prev) of atopic manifestations at age 4 in 65 children of mothers practicing food allergen avoidance during lactation (D) and 50 children of mothers not on food restrictions (ND)

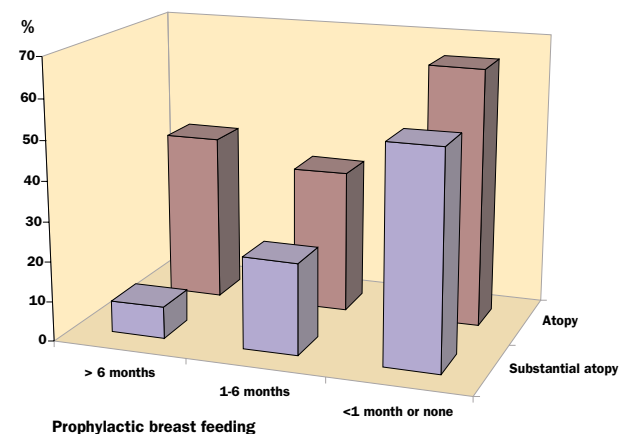
Atopy	Group	Cum Inc		Prev	
		No.	%	No.	%
Atopic dermatitis	D	<i>19</i>	<i>29</i>	<i>8</i>	<i>12</i>
	ND	<i>28</i>	<i>56</i>	<i>19</i>	<i>38</i>
Asthma	D	7	11	6	9
	ND	6	12	4	8
Bronchial obstruction	D	8	12	6	9
	ND	6	12	4	8
Rhinoconjunctivitis	D	8	12	8	12
	ND	5	10	4	8

Statistically significant differences (<.05) between values for the D and ND groups are in italics.

Adapted from: Sigurs N et al. Maternal avoidance of eggs, cow's milk, and fish during lactation: Effect on allergic manifestations, skin-prick test and specific IgE antibodies in children at age 4 years. Pediatrics 1992;89:735-39

FIGURE 1

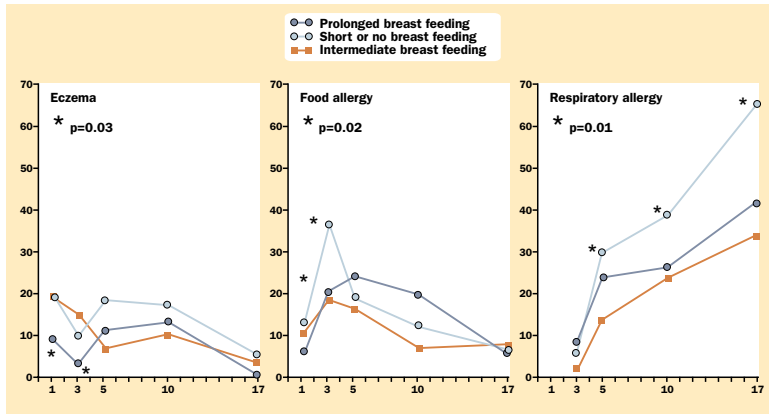
Prevalence of atopy and substantial atopy at the age of 17 years



Adapted from: Saarinen UM., Kajosaari M. Breast feeding as prophylaxis against atopic disease: prospective follow-up study until 17 years old. The Lancet 1995; 346: 1065-1069

FIGURE 2

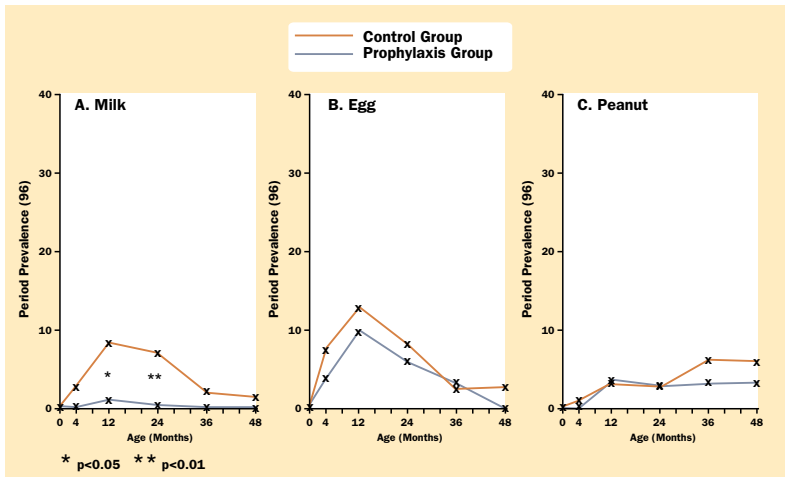
Prevalence of atopic eczema, food allergy and respiratory allergy in the infant feeding groups during follow-up for 17 years



Adapted from: Saarinen UM., Kajosaari M. Breast feeding as prophylaxis against atopic disease: □ prospective follow-up study until 17 years old. □ The Lancet 1995; 346: 1065-1069

FIGURE 3

Period prevalences of food SPT from birth to 4 years in prophylactic-treated and control groups



Adapted from: Zeiger RS. *et al.* Genetic and environmental factors affecting the development of atopy through □ age 4 in children of atopic parents: a prospective randomized study of food allergen avoidance. □ *Pediatr Allergy Immunol* 1992; 3: 110-27

infants whose mothers avoided egg, cow's milk and peanut during the last trimester of pregnancy and the whole lactation period (3, 4). The children themselves avoided cow's milk until the age of 1 year, egg until age 2 years and peanut and fish until age 3 years. The control group followed standard feeding practices.

The parents in both groups were encouraged not to smoke.

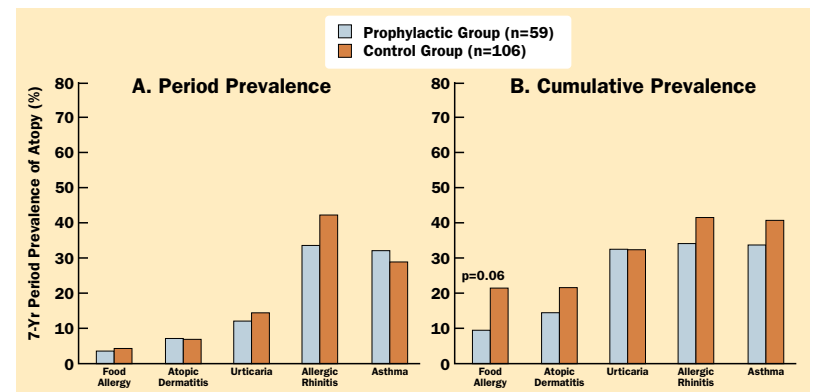
A higher 1- and 2-year period prevalence of cow's milk SPT was observed in the control group compared to the prophylactic-treated group. At 3 and 4 years of age, however, the prevalence had declined to similar levels in both groups. The period prevalence of other food allergens (Fig. 3A-C) and aeroallergens tested were similar during all time evaluations.

Despite a significant reduction in food allergy before the age of 2 years, no difference regarding food allergy, atopic dermatitis, allergic rhinitis, asthma or any atopic disease was observed between the groups at the age of 7 years (Fig. 4A and B). The authors conclude that food allergy without concurrent aeroallergen avoidance during infancy fails to affect atopic respiratory disease later in childhood.

This was studied in the Isle of Wight study reported below.

FIGURE 4

The 7-year period (A) and cumulative (B) prevalences of atopic disorders in prophylactic-treated and control groups



Adapted from: Zeiger RS. *et al.* The development and production of atopy in highrisk children: Follow-up at age □ seven years in a prospective randomized study of combined maternal and infant food allergen avoidance. □ *J Allergy Clin Immunol* 1995; 95: 1179-90

TABLE 2**Clinical manifestation and positive skin test at the age of 4 years**

Manifestation	Prophylactic (n=58)	Control (n=62)
Total allergy	19	34
Asthma	14	22
Eczema	8	15
Rhinitis	6	11
Food intolerance	3	7
Positive skin test		
House dust mite	3	15
Grass pollen	3	9
Cat	1	7
Dog	2	4
Mould	1	10
Milk	0	3
Egg	2	4

Adapted from: Hide DW et al. Allergen avoidance in infancy and allergy at 4 years of age. *Allergy* 1996;51:89-93

TABLE 3**Effect of smoking on prevalence of certain allergic disorders at 12 months of age**

Risk factor	Reference group	Odds ratio Asthma	Odds ratio Eczema	Odds ratio Food intolerance
Parental smoking				
Either	Neither	3.33	2.35	1.46
Both	Neither	11.0*	0.88	5.72

*p<0.005

Adapted from: Arshad SH et al. Effect of allergen avoidance on development of allergic disorders in infancy. *Lancet* 1992;339:1492-97

BY DIET AND AEROALLERGENS

In a cohort of children, at high risk of atopy from the Isle of Wight study, dietary and environmental prevention was applied to reduce the manifestation of atopic disease (6, 7, 8).

The prophylactic group was either breast-fed or given extensively hydrolyzed formula and the mothers excluded dairy products, egg, fish and nuts. In addition, acaricide was applied to their homes to reduce the exposure of house dust mite. The control group was fed conventionally and no environmental measures were taken.

Clinical manifestation of allergy was registered at 1, 2 and 4 years of age. There was significantly less total atopy in the prophylactic group than in the control group. A difference was also found in the number of positive SPTs between the two groups (Table 2). Parental smoking was found an important risk factor for the development of atopic disease in both groups, irrespective of whether only one or both parents smoked in the house (Table 3).

The authors conclude that a dual approach to the prevention of allergic disease, avoiding as far as possible sensitization to food and aeroallergens, significantly reduces the risk of atopic disease. However, this should be reserved for infants at very high risk of atopy, and close medical and dietetic supervision must be available.

The general primary prevention measures, which are suitable for everybody and could be recommended, are: breast-feeding in infancy and introduction of solid food after the fourth month of life, and the avoidance of smoking and passive smoke exposure of children.

SECONDARY PREVENTION

The effectiveness of allergen reduction was first suggested by studies in which patients were removed from their homes to a “low-allergen environment”, and later by allergen reducing measures in the homes of asthmatics.

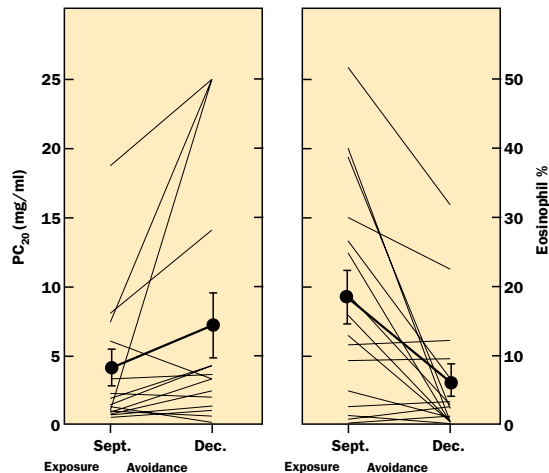
BY LIVING AT HIGH ALTITUDE

The influence of natural allergen avoidance at high altitude has also been evaluated in an Italian study. Asthmatic children spent their summer vacations at their homes at low altitude in the northeastern region of Italy (9). However, the school period from September to December was spent at high altitude in the Alps. At the end of the avoidance period of three months bronchial hyperreactivity (BHR) decreased, measured by an increase in PC₂₀. At the same time the number of eosinophils in sputum decreased, a sign of airway inflammation improvement (Fig. 5).

The effect of mite-allergen avoidance on epithelial damage in asthmatic children was examined in a similar study (10). The children, all mite sensitized within their homes at low altitude, spent the school

FIGURE 5

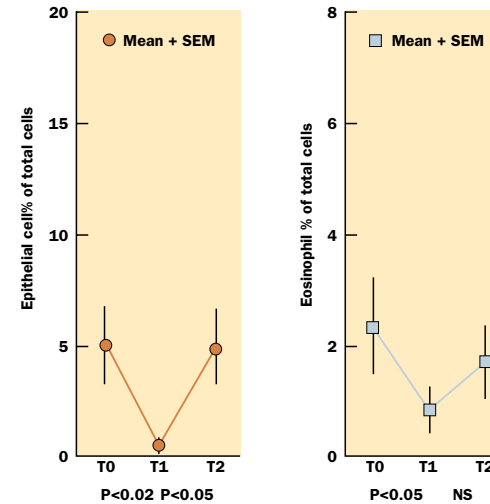
Individual changes for PC₂₀ and eosinophil percentage of total cells in the sputum before and after allergen avoidance. Thick lines show changes in the study population, expressed as means + SEM



Adapted from: Piacentini GL. *et al.* Influence of allergen avoidance on eosinophil phase of airway inflammation in children with allergic asthma. *J Allergy Clin Immunol* 1996; 97: 1179-84

FIGURE 6

Changes for bronchial epithelial cell percentage of total cells and eosinophil percentage of total cells in the sputum



Adapted from: Piacentini GL. *et al.* Mite-antigen avoidance can reduce bronchial epithelial shedding in allergic asthmatic children. *Clin Exp Allergy* 1998; 28: 561-67

period at high altitude in the Italian Alps with no mite contamination. After avoidance the percentage of epithelial cells decreased significantly only to increase again after 3 weeks of re-exposure to mite (Fig. 6).

Fifteen children, 8 to 15 years of age and with perennial unstable asthma and elevated specific IgE antibodies against house dust mite, were hospitalized in a high altitude clinic in the Swiss Alps (Davos) (11). After five weeks of allergen avoidance T-cell activation was reduced, the number of peripheral eosinophils decreased significantly and the lung function, measured as PEF and FEV₁, improved. Therefore, the authors stress the importance of identifying the specific cause of asthma in individual patients, as avoidance has a therapeutic significance.

BY ALLERGEN REDUCTION IN THE HOME ENVIRONMENT

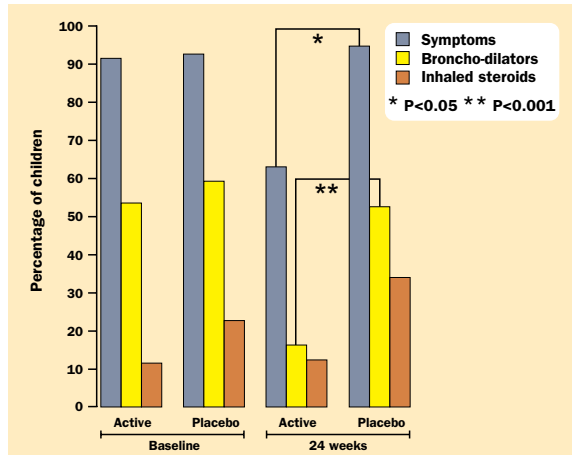
Several studies have been performed to reduce the home exposure of house dust mite in families with asthmatic children.

A study from UK recruited asthmatic children, sensitive to mites and with mite allergen in their mattresses (12). In the active group the children's bedrooms were treated with an acaricide and mattresses, pillows and duvets encased in exclusion covers. The control group received placebo treatment. Applying bedding covers and acaricide treatment led to a 100% reduction in mite allergen on the mattress, compared to a 53% reduction in the control group by 6 weeks. By 24 weeks the actively treated children had improved the FEV₁ and had fewer reported asthmatic symptoms than the controls (Fig. 7).

Progression of asthma was followed over 1 year in children whose homes received standard control intervention and compared with those whose homes received aggressive intervention for dust mite eli-

FIGURE 7

Percentage of children reporting symptoms and use of medications at least once during each 2 week period



Adapted from: Carswell F. *et al.* The respiratory effects of reduction of mite allergen in the bedrooms of asthmatic children - a double-blind controlled study. *Clin Exp Allergy* 1996; 26: 386-96

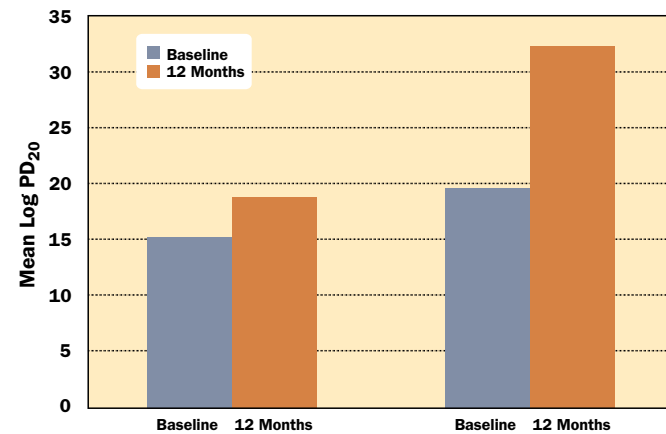
mination (13). Aggressive intervention consisted of the application of dustmite impermeable covers and tannic-acid application to the bedroom and living-room carpets. Dust mite levels decreased in the aggressive intervention homes compared with the standard intervention homes ($p<.05$). The standard group showed a mean increase in PD₂₀ of 24.2%, whereas the aggressive intervention group showed a mean increase of 63.3% ($p<.05$), (Fig. 8).

To evaluate the effect of mite elimination on preventing mite sensitization in infants with atopic dermatitis and food allergy a study was performed by a Japanese group (14). The infants were divided in two groups according to a reduction cleaning scheme; strict mite avoidance (mite counts <100 /g dust), and control group (mite counts 200-2100/g dust). Both groups were followed for one year. Only two of the 11 children in the strict-avoidance group had increased specific IgE concentrations compared to 8 of 12 in the control group (Fig. 9).

The preventive effect of bedding encasement on mite sensitization was evaluated in Japanese infants with atopic dermatitis and high

FIGURE 8

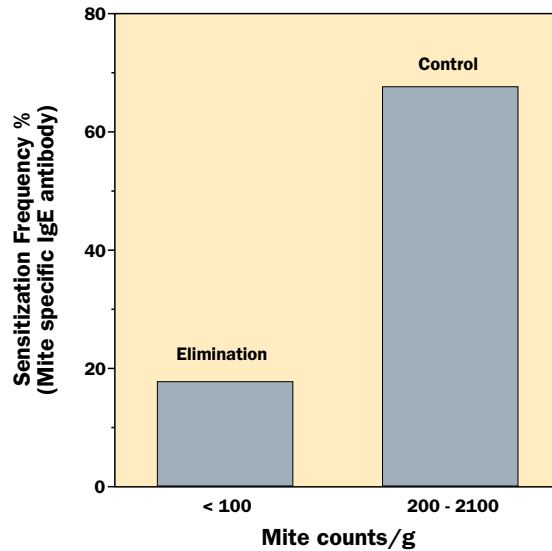
Changes in mean PD₂₀ before to 12 months after initiation of dust mite intervention



Adapted from: Shapiro GG. *et al.* House dust mite avoidance for children with asthma in homes of low-income families. *J Allergy Clin Immunol* 1999; 103: 1069-74

FIGURE 9

Effect of mite elimination in preventing sensitization and asthma attacks in atopic susceptible infants



Adapted from: Sasaki S. *et al.* Effect of mite elimination in preventing sensitization and asthma attacks in atopic susceptible infants. *J Allergy Clin Immunol News* 1994; Suppl 2: 471

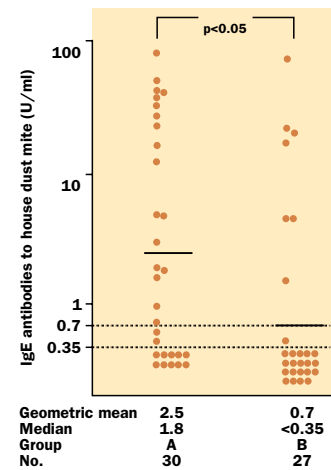
levels of IgE antibodies to either egg white, cow's milk or soybean, but not to mite (15). Thirty families were instructed to control the indoor environment, whereas 27 families were further guided to use encasings with microfibre fibres for quilts and mattresses. After one year the house dust mite levels in the mattresses was significantly reduced in the families with bedding encasing compared to the families without ($p<.001$). A significant difference in IgE antibodies to house dust mite was also seen between the two groups after one year, 0.7 U/ml with encasings and 2.5 U/ml without ($p<.05$), (Fig. 10).

BY FOOD ELIMINATION AFTER DISEASE DEVELOPMENT

A number of studies have evaluated the effect of dietary elimination in the treatment of atopic dermatitis. In a randomized controlled

FIGURE 10

Levels of IgE antibodies against house dust mite between two groups at the end of the study
Horizontal bars indicate geometric means

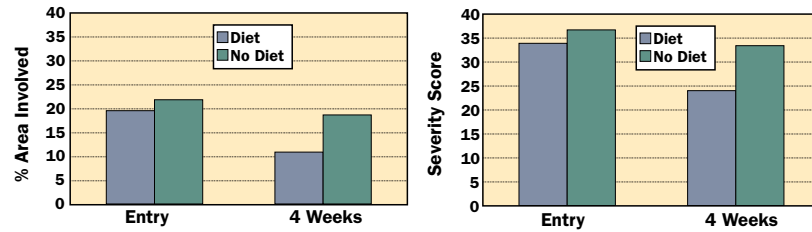


Adapted from: Nishioka K. *et al.* Preventive effect of bedding encasement with microfibre fibers on mite sensitization. *J Allergy Clin Immunol* 1998; 101: 28-32

study 55 children, under age 2 years, with atopic dermatitis and sensitive to eggs, identified by elevated specific IgE to eggs, were included (16). The children were randomized either to an egg exclusion diet or to a control group with no diet restrictions. General advice on care of eczema was given to both groups and both groups continued conventional topical treatment. After a 4-week regimen the mean reduction affected area by eczema was significantly greater ($p=0.02$) in the group on egg exclusion diet (19.6% to 10.9%) than in the control group (21.9% to 18.9%). A significant improvement was also observed in severity score ($p=0.04$); from 33.9 to 24.0 units for the diet group compared to 36.7 to 33.5 units in the control group (Fig. 11). The study suggests that advice on dietary exclusion is useful as part of the overall management of young children with atopic dermatitis.

FIGURE 11

Area involved and severity score in children with atopic dermatitis on egg exclusion diet or non exclusion diet



Adapted from: Lever R. *et al.* Randomised controlled trial of advice on egg exclusion diet in young children with atopic eczema and sensitivity to eggs. *Pediatr Allergy Immunol* 1998; 9: 13-19

TABLE 4

Number of children who presented onset of asthma during the one year study

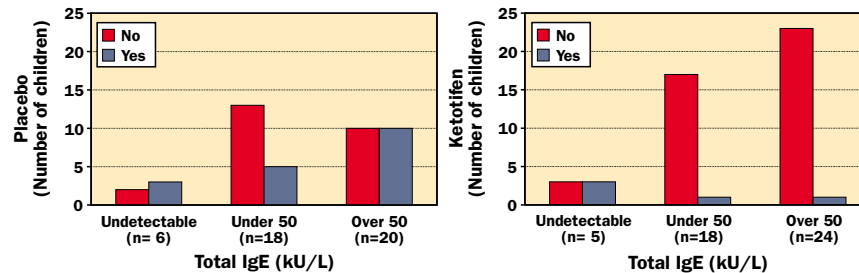
	Onset of asthma		Total	% Yes
	Yes	No		
Ketotifen group	8	53	61	13.1
Placebo group	25	35	60	41.6
Total	33	88	121	27.3

$\chi^2=p<.001$

Adapted from: Iikura Y *et al.* Prevention of asthma by ketotifen in infants with atopic dermatitis. *Ann Allergy* 1992;68:233-36

FIGURE 12

Onset of Asthma



Adapted from: Iikura Y. *et al.* Prevention of asthma by ketotifen in infants with atopic dermatitis. *Ann Allergy* 1992; 68: 233-36

TERTIARY PREVENTION

BY PHARMACOLOGY

The prophylactic effect of ketotifen against the onset of asthma was evaluated in 121 infants in Japan (17). All children had diagnosed atopic dermatitis but no history of asthma. The active group was treated with ketotifen and the control group was given placebo.

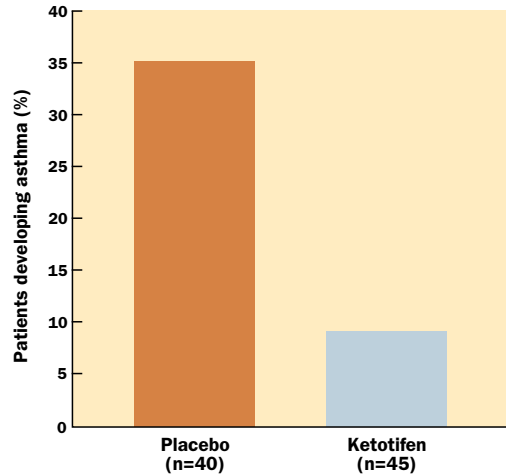
During the study period of 1 year, 13.1% of the children in the ketotifen group developed asthma compared to 41.6% in the placebo group (Table 4). There was no difference in the onset of asthma between the active and placebo treated groups in children with total IgE levels <50 IU/ml. A significant difference was, however, registered in children with IgE levels >50 IU/ml (Fig. 12).

In a study from Argentina the effect of ketotifen in preventing the onset of asthma was evaluated in 100 infants (18). The children had a strong family history of allergy and high levels of serum IgE but no diagnosed atopic disease. The children were treated either with ketotifen or placebo. At the end of the study period of 3 years, 9% of the children in the ketotifen treated group had developed asthma compared to 35% in the placebo group (p=.003) (Fig. 13). The results of aeroallergen skin tests were, however, not significantly different between the groups, which suggests that ketotifen acts by suppressing the bronchial inflammatory response and not by preventing sensitization.

The ETAC study included 817 infants, aged one to two years from 13 countries, suffering from atopic dermatitis and with at least one family member with a history of atopy (19). The infants were treated for 18 months with either cetirizine or placebo. Overall there was no statistically significant difference between the number of children who developed asthma when receiving cetirizine or placebo. However, subgroup analysis showed, that infants with raised total IgE levels or specific IgE antibodies and who received cetirizine had a reduced risk of developing asthma compared to those infants with raised baseline IgE, who received placebo. This reduction was observed for all specific IgE measured but reached significance for grass

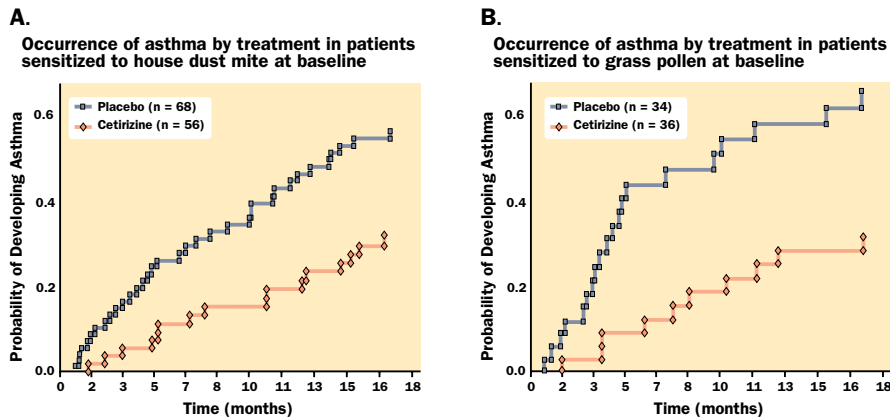
FIGURE 13

Percentage of patients who developed asthma during 3 years of treatment with ketotifen or placebo



Adapted from: Bustos GJ. *et al.* Prevention of asthma with ketotifen in preasthmatic children: a three-year follow-up study. *Clin Exp Allergy* 1995; 25: 568-73

FIGURE 14



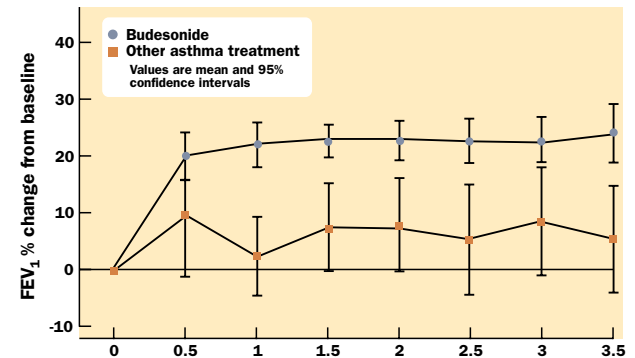
Adapted from: ETAC Study Group. Allergic factors associated with the development of asthma and the influence of cetirizine in a doubleblind, randomised, placebo-controlled trial: First results of ETAC. *Pediatr Allergy Immunol* 1998; 9: 116-24

pollen and house dust mite (Fig. 14A and B). The group proposes this treatment as a pharmacological intervention strategy to prevent the development of asthma in specifically sensitized infants with atopic dermatitis. An early correct diagnosis of sensitization is thus of highest urgency.

The effect of therapeutic intervention on the outcome of asthma in children has been evaluated in a longitudinal study in Denmark (20). Two hundred and sixteen children with asthma were followed for 1 to 2 years without inhaled budesonide and then for 3 to 6 years on inhaled budesonide. Sixty-two children with other anti-asthma treatment but no inhaled steroids were followed as controls. FEV₁ improved significantly during budesonide treatment, both compared

FIGURE 15

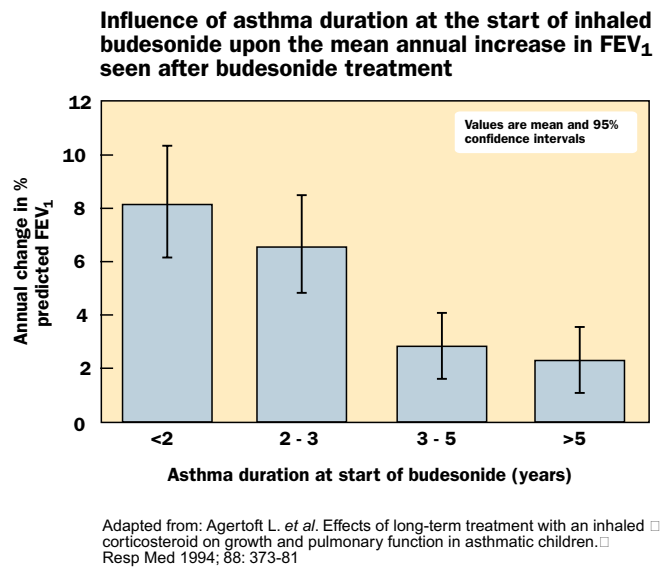
Changes in lung functions from the run-in period in children with inhaled budesonide and in children with other asthma treatment



Adapted from: Agertoft L. *et al.* Effects of long-term treatment with an inhaled corticosteroid on growth and pulmonary function in asthmatic children. *Resp Med* 1994; 88: 373-81

with the run-in period and with the control group ($p < .05$) (Fig. 15). Furthermore, there was a significant ($p = .01$) relationship between the duration of asthma at the start of budesonide and the annual increase of in FEV₁ during budesonide therapy. Children who started this treatment later than 5 years after the onset of asthma had significantly lower FEV₁ than the children who received budesonide within the first 2 years after the onset of asthma ($p < .05$) (Fig. 16). The authors conclude that early intervention with inhaled steroids may prevent the development of irreversible airway obstruction and reduce the risk of under-treatment.

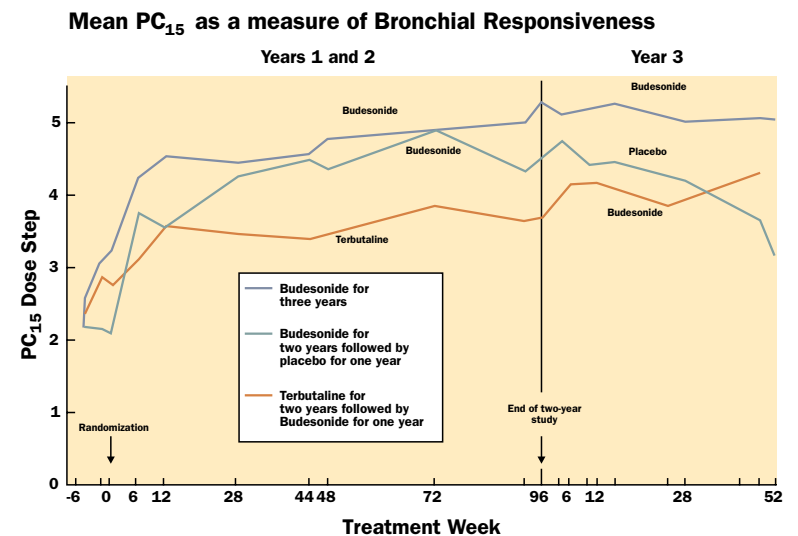
FIGURE 16



A Finnish two-stage, multicenter study of early intervention with inhaled steroid therapy looked specifically at the effect on patients with newly diagnosed asthma (21). There were 103 patients included with a duration of asthma of less than one year. The patients were randomised to either budesonide or terbutaline treatment and followed for two years. Budesonide was more effective than terbutaline in improving peak expiratory flow and more effective in reducing the symptoms of asthma.

After the first two years of treatment the study was continued for a third year to investigate whether the steroid dose could be reduced or discontinued and what effects could be expected from the cross-over of patients from β_2 -agonist therapy to corticosteroid therapy (22). The results in bronchial responsiveness during years 1, 2 and 3 are shown in Figure 17. At the end of the 3rd year bronchial responsiveness was maintained in 74% of the patients with a reduced dose of budesonide but in only 33% of the patients receiving placebo. The

FIGURE 17



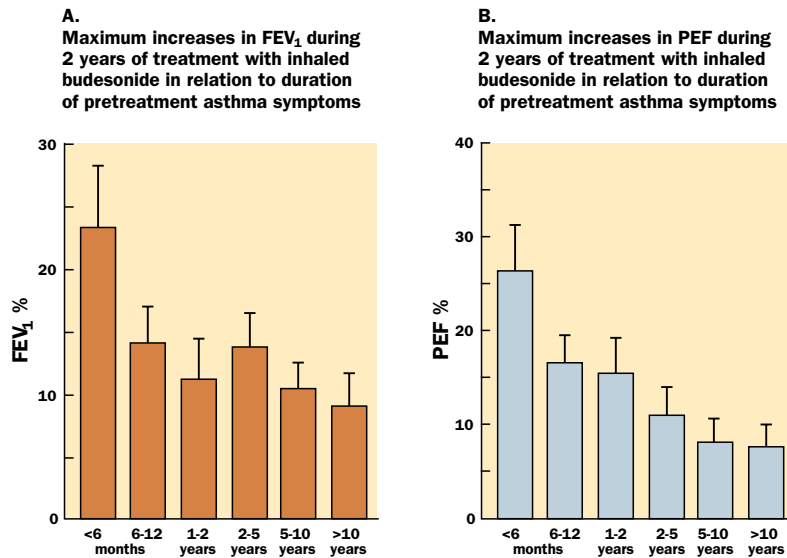
patients who crossed from terbutaline to budesonide improved, but less than the patients who started on budesonide at the beginning of the study. This study confirms that early diagnosis and treatment with inhaled steroids results in long-lasting control of mild asthma.

Another Finnish study aimed to define early intervention by examining the effect of inhaled corticosteroids in patients with varying duration of asthma symptoms before the initiation of therapy (23). According to duration of symptoms the 105 patients were divided in 6 groups. All patients were given inhaled corticosteroids for 2 years and lung function was registered after 3 months, 1 year, and 2 years. In the groups of patients with a duration of symptoms <2 years, mean FEV₁ and PEF were significantly higher as compared with the base line and as compared with the groups of patients with a longer duration of asthma symptoms (Fig. 18A and B). The results from this study also emphasize the importance of an early, correct diagnosis in order to intervene early during the progress of the disease.

Results from the studies above suggest that:

- Allergy testing is prerequisite for proper classification and specific treatment of allergic disease, in which avoidance of relevant—mainly indoor—allergens may greatly improve the prognosis.
- Avoiding exposure to relevant allergens is the logical way to manage allergic disease when the offending allergen can be identified and effective avoidance is feasible. In addition, a smoke-free environment should be established.
- A significant reduction in asthma symptoms and airway hyperresponsiveness could be obtained by early therapeutic intervention.
- Early diagnosis and early intervention by avoidance and/or proper treatment may thus prevent the progression of the allergic disease.

FIGURE 18



Adapted from: Selroos O. *et al.* Effect of early vs late intervention with inhaled corticosteroids in asthma. *Chest* 1995; 108: 1228-34.

ABBREVIATIONS AND DEFINITIONS

Substantial allergy

Atopic disease affecting more than a single organ, with more than one verified group of causative agents, duration of symptoms exceeding that of pollen season, and symptoms severe enough to require daily medications prescribed by the doctor.

BHR

Bronchial hyperresponsiveness.

FEV₁

Forced expiratory volume in 1 second.

PEF

Peak expiratory flow.

PC₂₀

The provocation concentration of histamine or methacholine causing a fall of 20% from baseline in FEV₁.

PD₂₀

The provocation dose of histamine or methacholine causing a fall of 20% from baseline in FEV₁.

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