

Review

Secondary prevention of allergic disease: an adjunct to primary prevention

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A particular urgency exists to identify strategies (interventions) that promote allergy prevention due to the formidable increase in both the prevalence and morbidity of atopic disease that is occurring worldwide. Genetic and immunologic manipulation of the high-risk atopic may surely provide future promising allergy prevention modalities. Presently, environmental engineering, in which actions are taken to reduce both allergenic and adjuvant exposure, particularly in high risk subjects, remains the available intervention strategy.

The first controlled effort to prevent atopy by allergen avoidance dates back almost 60 years to the study of Grulee & Sanford (1) that demonstrated that eczema in infancy was reduced almost 7-fold in a cohort of nearly 20,000 infants fed breast rather than cow milk. Despite numerous subsequent studies, passion and controversy still exist regarding the efficacy of allergy prevention due to the complexity of performing a definitive study. Allergy prevention until now has been directed at primary prevention (atopy prevention through the abrogation of primary IgE or other immunologic sensitization). These efforts, as discussed earlier, have often generated conflicting results, although consensus at this time appears to support the benefit of certain specific food

allergen avoidance measures (prolonged breast feeding for more than 4 months, hypoallergenic protein hydrolysates during supplementation/weaning, and delaying solid foods until after 6 months) in the prevention of food, G1 allergy and atopic dermatitis within the first 2 years of life (Table 1) (2). With respect to primary aeroallergen allergy prevention, the only study thus far tackling this problem, noted that acaricide application and use of polyvinyl encasings added to food allergen avoidance appeared to significantly reduce asthma at 1, but not 2, years and food or inhalant sensitization by 2 years (3).

Stages of allergy prevention

Regarding the secondary prevention of allergy (deterrence of disease expression despite prior IgE sensitization), there exists no controlled study that would help one to determine whether such efforts would be likely to garner success or frustration. Help in this regard may derive from results of studies which have examined tertiary allergy prevention (suppression of symptoms despite the occurrence of atopic disease). Though primary prevention is optimal, secondary prevention may be instituted to supplement primary prevention and serve as a fall-back

Table 1. Prospective randomized controlled studies of the effect of food allergen avoidance on the development of atopic disease in infants of atopic parents

Study (Reference)	Subjects (n)	Mom Pregnancy Diet	Mom Lactation Diet	Infant Diet	Follow-up	SPT/RAST	DBPCFC	Atopic Disease	Comments
Magnusson, et al. (39-41)	197	3rd trimester (No egg, CM) vs No restriction	None	Breast +/- or casein hydrolysate (3 Mo); Solids (> 4 Mo); CM (> 6 Mo); egg/fish (> 9 Mo)	5 Yr	Not significant	No	Not significant	Pregnancy diet had no effect on infant atopy, SPT, or IgE
Lilja, et al. (42, 43)	162	3rd trimester (No egg, CM) vs No restrictions	None	Exclusive breast (5-6 Mo) vs No restrictions	1.5 Yr	Not significant	No	Not significant	Pregnancy diet had no effect on infant atopy, SPT, or IgE
Chandra, et al. (44)	71	Entire pregnancy (No egg, CM, fish, peanut, beef) vs No restrictions	Entire lactation (Same as pregnancy) vs No restrictions	Exclusive breast (5-6 Mo) vs No restrictions	1 Yr	Not determined	No	Reduced AD Severity by 1 Yr*	No immunologic or food challenge confirmation. Benefit probably derives from infant diet and/or maternal lactation diet and not pregnancy diet
Zeiger, et al. (8, 37)	288	3rd trimester (No egg, CM, peanut) vs No restrictions	Entire lactation (Same as pregnancy) vs No restrictions	Breast +/- or casein hydrolysate (12 Mo); Solids (> 6 Mo); CM, soy, corn (> 12 Mo); egg, fish, peanut (> 24 Mo) vs AAP guidelines	7 Yr	Reduced CM-IgE prevalence at 1* and 2 Yr**	Yes; half consented, 80% positive challenges	Reduced current prevalence of AD* and food allergy** at 1 yr. Asthma and AR unaffected by 7 Yr	Benefits probably derive from infant diet and/or maternal lactation diet and not pregnancy diet (see Magnusson and Lilja above)
Hattewig, et al. (45-47)	115	None	1st 3 Mo of lactation (no egg, CM, fish) vs No restrictions	Breast +/- or casein hydrolysate (6 Mo); CM/solids (> 6 Mo); egg/fish (> 9 Mo)	4 Yr	Reduced no. of CM +/- or egg-IgE tests at 3 Mo**	No	Reduced AD at 3**, 6*, and 48** Mo	Groups assigned by hospital rather than by true randomization
Chandra, et al. (48)	97	None	Entire lactation (No egg, CM, peanuts, soy, fish) vs No restrictions	Exclusive breast (~ 6 Mo), Solids (~ 6 Mo)	1.5 Yr	Not determined	No	Reduced AD by 1.5 Yr*	No immunologic or food challenge confirmation
Chandra, et al. (48)	124 (3 group)	None	None	Exclusive casein hydrolysate vs CM or soy. No breast feeding	1.5 Yr	Not determined	No	Reduced AD* by 1.5 Yr with casein hydrolysate	AD prevalence exceptionally high; no immunologic or food challenge confirmation
Chandra, et al. (49, 50)	288 (4 group)	None	None	Exclusive partial whey hydrolysate (6 Mo) vs CM, soy, or breast feeding X 6 Mo	1.5 Yr	No difference in CM-IgE at 2 and 6 Mo	No	Reduced 6 and 12 Mo AD cumulative prevalence*	No immunologic or food challenge confirmation; Cord blood + CM/ Soy-IgE unexplainably high incidence
Lucas et al. (51)	75 (Preterm)	None	None	Human milk vs preterm formula X 1.5 mo	1.5 Yr	Not determined	No	Reduced AD by 1.5 Yr*	No immunologic or food challenge confirmation. Only randomized study of human milk compared to CM feedings

Table 1. (Cont)

Study (Reference)	Subjects (n)	Mom Pregnancy Diet	Mom Lactation Diet	Infant Diet	Follow-up	SPT/RAST	DBPCFC	Atopic Disease	Comments
Vanderplas, et al. (52)	67	None	None	Partial whey hydrolysate vs CM 1 Yr formula x 6 Mo	1 Yr	No difference in CM-IgE at 2 and 6 Mo	Blinded but not DBPCFC	Reduced CMA/CMPI prevalences at 6** and 12* Mo	Exceptionally high 6 Mo prevalence of AD (77%) and CMA/CMPI (34%) in controls; CMA/CMPI during (n = 1) and after (n = 3) hydrolysate
Arshad, et al. (53, 54)	120	None	Entire lactation (No egg, CM, fish, nuts) vs No restrictions	Breast +/- soy hydrolysate (9 Mo); CM/soy (9 Mo); egg (11 Mo); all others (12 Mo) plus mite avoidance (acaricide and encasing) vs No restrictions	2 Yr	Not significant at 1 Yr; significantly reduced at 2 Yr	No	Reduced AD* and asthma* by 1 Yr; any atopy at 2 Yr	Control group with more smoking mothers (p = 0.11), but multivariate analyses confirmed benefit. Protective effect seen after exclusion of smokers
Malley/Henocq (55)	165	None	None	Pregestimil vs CM formula ± breast milk + no solids X 4 mo	4 Yr	Not determined	No	Reduced eczema at 4 mo (p = 0.07), 2 & 4 Yr (p < 0.01)	Dropout 25% at 1 Yr, no specific IgE or accounting for smoking, etc
Halken, et al. (56)	141	None	None	Breast (n = 20) Nutramigen (n = 59) vs Profylac (n = 62) and delayed solids and CM for 6 mo	1.5 Yr	CM-IgE in 4/5 with CMA/CMPI	Open challenge	CMA/CMPI = 1/20 vs 1/59 vs 3/62, in grps respectively	Overall CMA/CMPI = 3.6% vs 15/72 (20%) in similar 1985 cohort without allergy preventive efforts

Abbreviations: CM (cow milk), AD (atopic dermatitis), CMA (CM allergy), CMPI (CM protein intolerance), AR (allergic rhinitis), DBPCFC (double-blind, placebo-controlled, food challenge), Mo (month), Yr (year) *p < 0.05; **p < 0.01 (Modified from Zeiger RS. *Pediatr Allergy Immunol* 1994; 5 (suppl 2): 33-43.

position to families less interested in or committed to allergy prevention, and who require stronger and more immediate evidence of atopic risk. Moreover, secondary prevention could adapt prevention efforts "proven" effective in primary and tertiary prevention.

To judge the success of any preventive effort, certain requisites should be met including the ability to 1) predict the high-risk group, 2) demonstrate effective intervention strategies, 3) utilize acceptable interventions, 4) minimize adverse effects, and 5) generate cost-effective efforts.

Ability to predict the high-risk group postnatally

Part of the rationale which suggests that secondary prevention may serve as a real avenue for prevention stems from the relentless features of the "allergy march" in which certain, sometimes transient, atopic conditions or events often precede other more lasting or permanent ones. Most studies agree that the natural history of atopy (4) dictates that 1) atopic sensitization to foods precedes food allergy and aeroallergen sensitization, 2) food allergy and food and inhalant sensitization precede allergic rhinitis and atopic asthma, 3) atopic dermatitis and infectious asthma precede atopic asthma, 4) infectious asthma precedes atopic asthma, and 5) nasal eosinophils and basophilic cells precede allergic rhinitis. From this natural "atopic march", infants at high risk of developing atopy could be identified either 1) after development of an indicator atopic marker [specific food (egg)-IgE, aeroallergen-IgE, elevated serum IgE or nasal eosinophils/basophil], 2) after development of an indicator disorder (food allergy, atopic dermatitis, recurrent viral induced asthma in infants of atopic parents, or recurrent croup) and/or 3) presence of an atopic family history.

For example, a RAST $\geq 1+$ to egg at 8 months in an unselected cohort evidenced 32% and 50% sensitivities and 95% specificities for atopy, respectively, at 1.5 and 7 years, which were better predictors of atopy than earlier determined elevated cord blood IgE levels among the same cohort (5). Moreover, a positive ovalbumen-SPT (skin prick test) at age 6 months showed a 40% sensitivity and 95% specificity for 18-month atopic disease (6). These studies confirmed earlier findings which demonstrated that a positive egg-SPT in infancy predicted more severe atopic diseases and higher prevalences of allergic rhinitis and other food SPTs by 15 years (7). In a 7-year prospective study of the development and prevention of atopy in high-risk infants, we noted that a positive egg-SPT at or before age 1 year increased 2-3 fold the positive predictive value for both the 7-year current and cumulative prevalences of atopic dermatitis and allergic rhinitis (Zeiger RS et al., J

Table 2. Genetic, immunologic, and environmental risk factors and markers for the development of atopic disease

Genetic/immunologic/perinatal

- Family atopic history [biparental (> risk with maternal disease)]
- Increased cord blood IgE level
- RFLPs on chromosome 11q (general atopy), chromosome 7 (specific-IgE), and chromosome 5q (total serum IgE level)
- Increased cord IgE-binding factors (soluble FcRII)
- Increased total and specific-IgE (particularly egg) in infancy
- Decreased T cells (function) in cord blood and in infancy in high-risk infants
- Decreased cytokine gamma-interferon/IL-4 ratio in high-risk infants
- Increased blood eosinophilia or nasal eosinophilia/basophilia in infancy
- Increased monocyte phosphodiesterase activity
- Cord blood thrombopenia
- Increased cord blood linoleic acid
- Decreased breast milk long-chain polyunsaturated fatty acid levels
- Male gender and low birth weight

Environmental risk factors for atopic disease

- Specific Environmental Stimulation
 - Feeding practices
 - Brief breast feeding
 - Food allergens in breast milk
 - Early solid foods
 - Time of weaning
 - Magnitude of allergen exposure
 - Early allergen exposure (foods, mites, pets, month of birth)
- Non-specific environmental stimulation
 - Intrauterine exposure to drugs
 - Infections (viral and bacterial)
 - Passive tobacco smoke and pollutants
 - Tight-poorly ventilated houses
 - Household dampness

Allergy Clin Immunol, in press). In this same study, the presence, compared to the absence, of food allergy by age 2 years was associated with significantly higher 4-year cumulative prevalences of allergic rhinitis (odds ratio = 2.9) and of asthma (odds ratio = 2.2) (8). Family history of atopy with its 40% sensitivity and 80% specificity for predicting atopy at ages 7 and 11 years can also be used as an atopic predictor marker for secondary prevention identification (4).

From the above discussion, it could be argued that an efficient and cost-effective approach to allergy prevention would involve periodic prospective surveillance of infants (young children) for the clinical and immunologic expression of atopic sensitization or disease. The high-risk infant during well-baby visits could be identified by the responsible primary health-care team by ascertaining 1) atopic sensitization by performing SPT to foods such as egg and milk twice during infancy (4 and 12 months) and yearly to aeroallergens such as dust-mite (Der p I/Der f I mix), *Alternaria*/Cladosporium mix, cat (or dog), and grass mix beginning at age 1

year (alternatively, a screening serum assay could be used) and 2) atopic disease expression by recognizing recurrent infectious wheezing, eczema and food allergy. These high-risk infants could then be referred to allergy specialists for allergy prevention instruction and follow-up. Allergy preventive regimens that have proven effective for primary and tertiary prevention would be instituted in these high-risk infants. This approach would direct intensive preventive efforts only for those infants who have demonstrated atopic sensitization or atopic disease in an attempt to prevent the "atopic march" as discussed above. Prospective studies will need to assess the efficacy and cost of instituting such a secondary allergy prevention program.

Atopic risk factors

Studies have identified multiple atopic risk factors which must be addressed with allergy preventive measures in order to prevent allergic disease and its progression. These interventions require implementation on both an individual and societal basis in order to successfully counter the worldwide allergy epidemic.

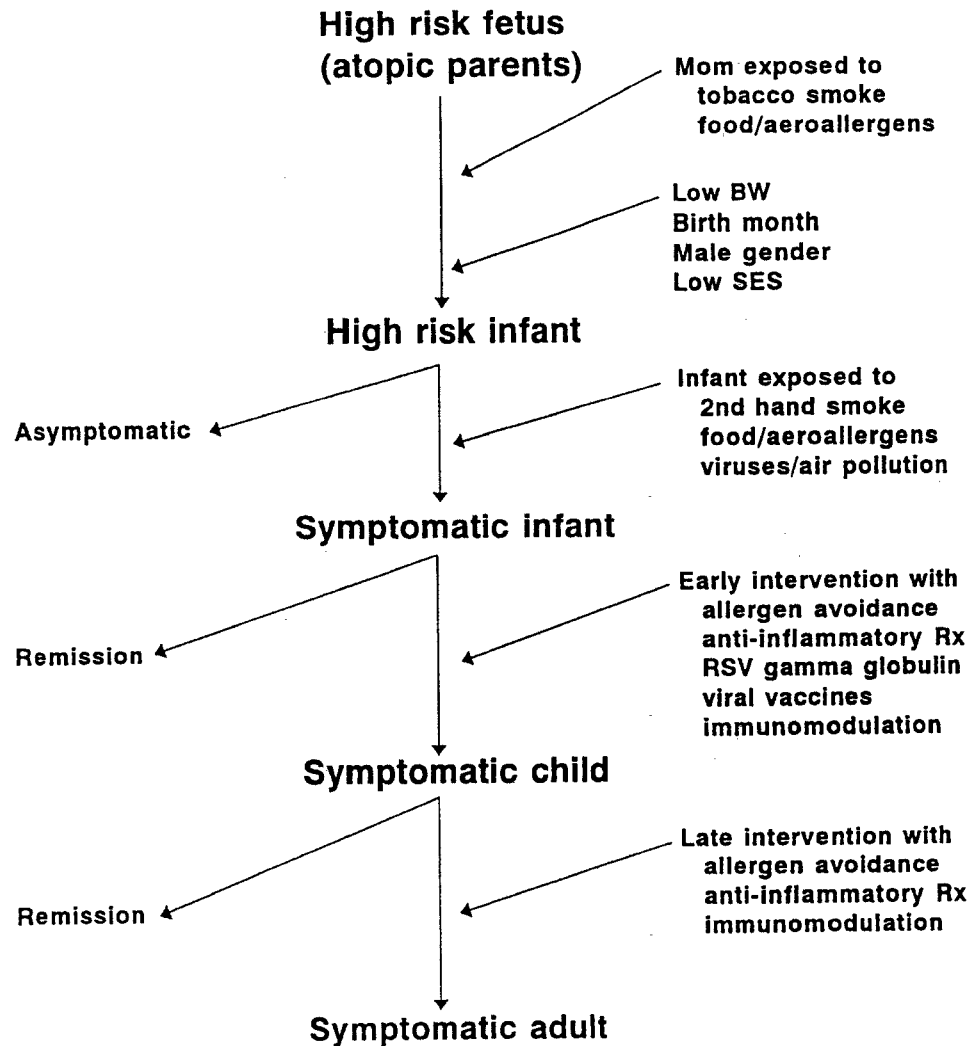
There may exist a particularly critical time early in infancy in which the genetically programmed infant may be more easily sensitized to exposed allergens under certain environmental conditions. Various perinatal genetic/immunologic and environmental factors and markers indicate an increased risk of the subsequent development of allergy (Table 2).

Modulation of major atopic risk factors

With respect to the institution of anti-allergy measures, certain major atopic risk factors such as atopic heredity, male gender, and non-white ethnicity are completely unmodulatable, while other factors such as birth month, low socio-economic status, and urban residence are relatively unmodulatable. Important atopic risk factors which are more modulatable include 1) raising low health consciousness, 2) reducing environmental pollution and tobacco exposure (ETS), 3) delaying introduction of allergenic foods during infancy, and 4) reducing household dust-mite and dander levels.

A recent editorial presented a useful schema for both the identification of high-risk infants and institution of preventive measures, many directed at secondary prevention (Fig. 1) (9). Although no study has shown that these interventions are useful for secondary allergy prevention, both intuition and their ameliorating effect in tertiary allergy prevention suggest strongly that later studies should be able to prove their utility in secondary prevention.

Fig. 1. Risk factors affecting the development of atopic disease from fetus to adult (modified from reference 9).



These measures include the reduction/elimination of 1) early food allergen exposure, 2) household dust-mite and dander levels, 3) occupational allergens/pollutants, 4) ETS, 5) air pollution, 6) RSV infections, and 7) the “atopic march” with allergy preventive medication or immunomodulation.

Early food allergen exposure

Risk factors – Food ingestion postnatally elicits a brisk humoral immunologic response involving specific antibody of all the immunoglobulin classes, including IgE. Early ingestion of potentially allergenic foods in the high-risk infant triggers a higher and more persistent specific and total IgE response which often leads to disorders including food allergy, atopic dermatitis and GI allergy (4). As summarized elsewhere, many studies have implicated early food allergen exposure in the development of food allergy.

Interventions – Although not specifically related to secondary prevention, one still must emphasize

the importance of promoting prolonged breast-feeding for all infants since human milk is the ideal source of nutrition, immunologic factors, intestinal maturation, and infant – mother bonding. Whether it definitely prevents food allergy remains to be settled, but the weight of the published data appears to support its protective effect, although conflicting studies exist. Its role in reducing infectious asthma during infancy has been cited and appears real, particularly for RSV infections, as it may transfer protective neutralizing RSV-antibodies (4).

Table 1 details the most recent controlled generally« randomized, primary prevention studies which as a group support the premise that food allergen avoidance during early infancy reduces the development of food, but not respiratory, allergy during early infancy up to age 2 years. Institution of some of these avoidance measures (hypoallergenic protein hydrolysate supplementation and delaying solid food introduction, particularly the more allergenic such as milk, egg, and peanut until after age 1 year or later) in secondary allergy prevention in infants after the

Table 3. Effect of various environmental factors on dust mite levels and sensitization

Residential factors increasing mite levels (57)

- Use of animal hair blankets
- Use of bed covers, underblankets, or older mattresses
- Dampness/high relative humidity
- Ground floor residence
- Poor ventilation

Effect of altitude (16, 17, 58)

- [Mite] vary inversely with altitude
- [Mite] decreases 90% at 1 km
- Serum IgE level and mite-IgE decrease ~ 50% at 1.4 km residence for 9 months
- Mite-specific basophil histamine release reduced
- PD₂₀ histamine improves after 1 year residence at Davos
- Serum markers of eosinophil activation decline at 1.8 km

Effect of hospitalization (18)

- Mite antigen levels 98% lower in hospital
- Serum IgE level and mite-IgE decline
- Peak flow and symptoms better
- Asthma medication reduced
- PD₂₀ histamine improved in > 75% of patients

Sensitization (11)

- Risk level for development of mite-IgE and asthma: 2 µg Der p I/gm dust
- Risk level for acute asthma: 10 µg Der p I/gm dust
- Age of first wheezing episode inversely correlated with highest mite antigen exposure during infancy
- Goal: reduce mite levels in homes below 2 µg Der p I (100 mites or 0.6 mg guanine)/gm dust

development of food-specific IgE or after disease development, as in tertiary prevention, certainly has merit, though unproven for secondary prevention.

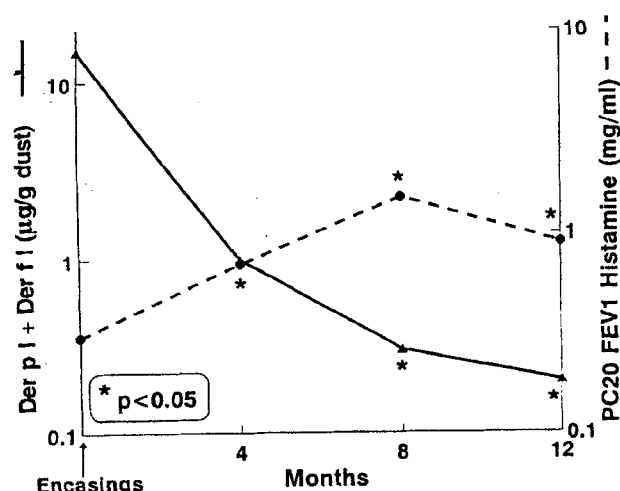


Fig. 2. Effect of covering mattresses, pillows, and comforters with polyurethane-lined cotton encasings on Der p I antigen levels and PC₂₀ FEV₁ histamine bronchial hyperreactivity in children with mild to moderate bronchial asthma, * $p < 0.05$ (compiled from reference 19).

Early aeroallergen exposure

Risk factors – 1, Housedust-mite. Exposure to elevated levels of Der p I in amounts exceeding 2 µg/g of dust in carpets and bedding measured during infancy has been related to both an increased prevalence of positive SPT and increased concentrations of Der p I specific-IgE by age 5 in high-risk infants (10). Additionally, Der p I levels in excess of 10 µg/g of household dust measured during infancy were associated with a 5-fold greater risk of developing asthma by age 11 (11). In this study the age of the initial wheezing episode was inversely related to the level of Der p I exposure at age 1 year in all subjects, particularly those found atopic. Other studies appear to support these findings with respect to increased mite sensitization with greater mite exposure (12); however, unexplained is the absence of mite specific-IgE in most of these subjects prior to age 2. It is proposed that early exposure primed these infants to develop sensitization with continued exposure later in childhood. Such an explanation fails to contend with the diametrically opposite situation with respect to food sensitization early in infancy, in which food allergen exposure leads to recognizable food IgE shortly after exposure, even when such exposure may be rather minimal (food allergens in breast milk or inadvertent exposure).

2) Other aeroallergens. Cat/dog exposure or cat Fel d 1 in homes during infancy is associated with sensitization to cat by age 1 year (13), dog by 9 years (14) and cat during childhood (15).

Interventions – Mite allergen levels are lower at higher altitudes (16, 17) and within hospitals (18). Residence in such environments (Table 3) (16–18) and use of allergen-proof encasings for the bedding (Fig. 2) (19) lead to improvements in asthma and BHR, and reduction in inflammatory and immunologic atopic markers (17). Practical allergen reduction measures (Table 4), which have been successful at reducing mite and dander levels in households during tertiary prevention, could be used in secondary prevention.

Occupational allergen exposure

Risk factors – More than 200 agents have been identified as causing occupational asthma and rhinitis. The atopic individual appears particularly at high risk of developing IgE sensitization to agents of high molecular weight to which they find themselves exposed at the workplace, including locust allergens, laboratory animal proteins, papain, *Bacillus subtilis* enzymes (alcalase), flour dust, and latex. Lack or absence of mechanisms to control emission or exposure to these allergens appears to be responsible for sensitization and disease (20). Two recent

Table 4. Practical house-dust mite and animal allergen reduction measures

House-dust mite (59–61)	Animal emanations-danders
Encase mattress/pillow with impermeable cover	Discourage indoor furry pets
Wash bedding weekly at 130°F	Wash pets weekly
Remove carpets, stuffed toys, clutter from bedroom	Ensure no carpets if pets present
Spray carpets with benzyl benzoate or tannic acid	Exterminate cockroaches
Encourage HEPA filtration	Spray carpet/furniture with tannic acid
Remove upholstered furniture	
Maintain home < 68°F/45% humidity	
Expose carpets to sunlight	

examples deserve mention. Of 81 workers in a latex surgical glove manufacturing plant, 11% demonstrated IgE sensitization and 6% experienced asthma due to latex (21). Soybean dust released during unloading into silos has caused major asthma epidemics in Barcelona, leading to increased hospitalizations and ICU admissions (22).

Interventions – Measures which successfully reduce exposure to occupational allergens in the workplace represent effective secondary allergy preventive efforts for the high-risk working atopic individual. The installation of filters on the silo prevented/reduced dissemination of airborne allergenic soybean dust more than 10-fold eliminating asthma outbreaks caused by soybean in Barcelona (22). In general, 1) improving ventilation systems, 2) designing workplaces to minimize allergen exposure, 3) installing effective filters, and 4) encouraging use of protective respiratory gear are some of the allergen control measures which industry needs to adopt in the attempt to reduce the increasing prevalence of occupationally induced atopic disease.

Table 5. Adverse effects of pre- and postnatal passive ETS exposure on children

A. Prenatal passive ETS
1. More low birth weight/low gestational age infants
2. Higher infant mortality
3. Reduced lung function
4. More infectious wheezing by age 1 year
B. Postnatal passive ETS
1. Reduced lung growth and FEV ₁
2. Greater bronchial hyperresponsiveness
3. More persistent wheeze
4. More exacerbations of asthma
5. Higher serum IgE levels
6. Greater prevalence of aeroallergen-IgE
C. 1993 Environmental Protection Agency report on passive ETS
1. Causes 150,000–300,000 LRI annually in < 18-month-olds
2. Increases both incidence and severity of asthma
3. Increases risk of new onset of asthma
4. Increases risk of serous otitis media

Environmental tobacco smoke (ETS) exposure

Risk factors – ETS exposure prenatally and postnatally causes major adverse atopic consequences, which have led to an EPA indictment of its danger (Table 5).

Recent disturbing facts concerning ETS have emerged, including the following: 1) adolescent ex-asthmatics harbor a strong intention to smoke, 2) 46% of asthmatics vs 28% of nonasthmatics smoke during pregnancy (24), 3) the usual advice fails to curtail smoking substantially during pregnancy, and 4) worldwide smoking remains at a high level despite decreases in some countries (Fig. 3) (25).

Interventions – International, national, and community strategies are required to combat ETS. In the USA aggressive efforts including 1) public educational campaigns on the hazards of ETS, 2) taxation on tobacco, and 3) prohibition of smoking in public places and workplaces have led to reductions in per capita consumption of cigarette packs per year from 1981 to 1990 in the USA as a whole of 23% (from 15.4 to 11.9) and in California of 34% (from 13.1 to 8.6) (26).

Exposure of the high-risk atopic to home ETS can be approached with structured counseling of smoking families. In collaboration with the San Diego State University School of Public Health, we have recently completed a randomized and controlled

Table 6. ETS reduction by counseling/behavioral modification in families of asthmatic children: Project Zephyr design (27)

Measures	Smoking families randomized		
	Counseling (n = 31)	Measurement control (n = 28)	Usual Rx control (n = 32)
ETS monitor	+	+	+
Interview	+	+	+
Symptom diary	+	+	+
Smoking diary	+	+	+
Counseling*	+		

*Counseling techniques: 1. recognize/record ETS, 2. brainstorm lowering ETS practices, 3. sign contingency contract, 4. generate personal feedback, and 5. shape and reinforce positive behaviors.

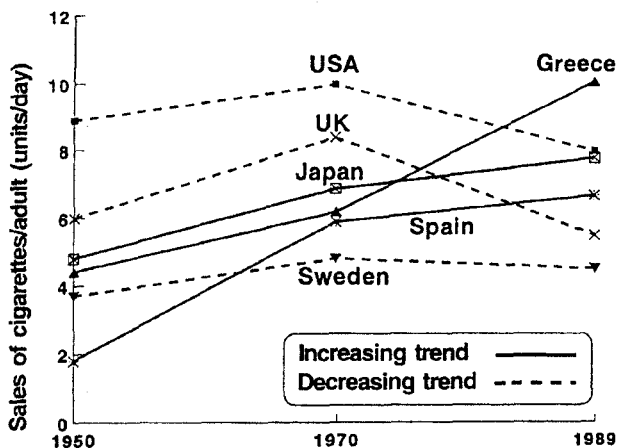


Fig. 3. Trends in cigarette sales over 4 decades in representative countries (compiled from reference 25).

study which compared behavioral counseling intervention with usual care and measurement control groups in 91 asthmatic children of smoking parents. The design and counseling techniques (Table 6) and outcome (Fig. 4) of the study (Project Zephyr) reveal that intensive behavioral modification can successfully reduce the daily exposure of children to their parents' smoke (27). Counseling parents on the hazards of ETS and actions to modulate it at home led to reductions in 1) parental smoking rates, 2) children's exposure to ETS, and 3) asthma symptoms at 2 months during the most intensive counseling intervention (27).

Atmospheric pollution exposure

Risk factors – Although not yet proven, it is quite probable that urbanization with its associated pollution holds some degree of responsibility for the in-

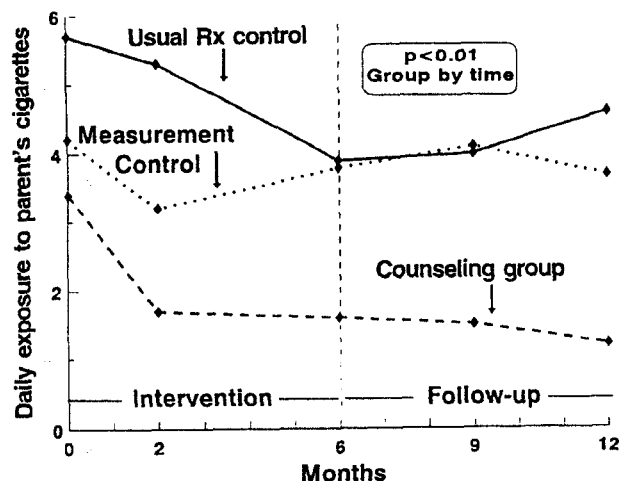


Fig. 4. Effect of intensive behavioral modification and counseling on exposure of asthmatic children to their parent's daily cigarette smoke (modified from reference 27).

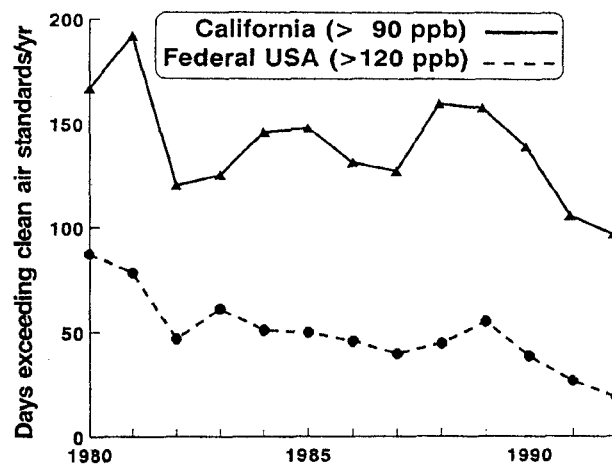


Fig. 5. Effect of implementation of Clean Air Standards legislation on San Diego air pollution from 1980 to 1992. Standards established by law: California < 90 ppb and Federal USA < 120 ppb (source: Air Pollution Control, District County of San Diego, Annual Report 1992).

crease in the worldwide severity and perhaps even prevalence of atopic disease. Just a short list of associations of pollution with atopy raise the specter of its impact or danger: 1) high concentrations of ozone increases bronchial hyperresponsiveness (BHR) (28), 2) ozone in concentrations of 120 ppb increases BHR to allergen (29), 3) diesel fumes increase cedar pollinosis in Japan (30), 4) polluting paper pulp plants increase BHR and asthma (31), and 5) oxides of ozone increase sensitization to allergen in guinea pigs (32).

Interventions – Like anti-ETS strategies, anti-pollution measures need to be adopted internationally, nationally, and regionally. In California measures which have led to reductions in ozone include 1) establishment of Air Quality Control Districts and Boards, 2) legislation to promote clean air (Califor-

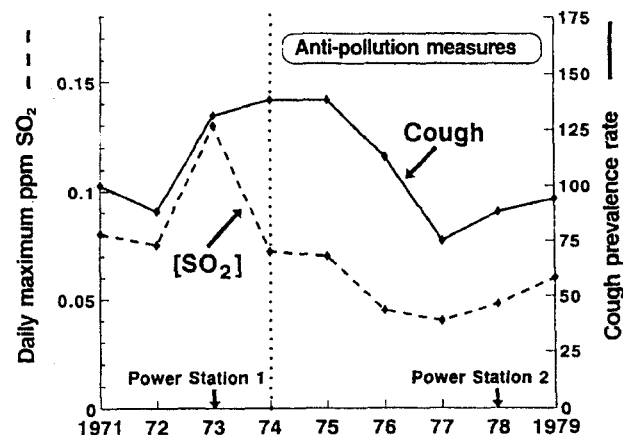


Fig. 6. Effect of implementation of anti-pollution measures on reducing both sulfur dioxide concentrations and cough prevalence in atopic children after installation of a polluting power station had increased both parameters (compiled from reference 33).

Table 7. Effect of economic status on instituting mite control procedures (38)

Measure	Compliance with measures (%)	
	Low income (n = 30)	High income (n = 30)
Encase bedding	40%	73%*
Air filter/condition	20%	53%*
Remove toys	67%	40%
Damp dust	83%*	50%

*p<0.02

nia and Federal Clean Air Acts of 1988 and 1990), 3) emission controls on automobiles, 4) car pooling, and 5) control or restriction of polluting manufacturing plants. These measures have led to significant reductions in days of pollution in excess of USA and California standards in San Diego from 1980 to 1992 (Fig. 5). Implementation of anti-pollution measures reduced both SO₂ levels and cough prevalence in atopic children in whom installation of a polluting power station had aggravated both parameters (Fig. 6).

Viral infections

Risk factors – Viral infections may affect atopic disease by 1) acting as polyclonal B-cell activators of IgE antibodies (Epstein-Barr virus), 2) increasing BHR and lower respiratory illnesses in dogs and man (canine adenovirus and parainfluenza virus), 3) priming for recurrent wheezing in infancy (RSV), and 4) increasing atopic sensitization during infancy (4).

Interventions – Prevention of RSV infection in high-risk infants would probably reduce the prevalence of viral-induced wheezing in infancy and potentially affect the development of asthma. High-titer RSV immunoglobulin administered preventively to high-risk respiratory and cardiac infants success-

fully reduced lower respiratory tract infections caused by RSV (34). Several potential measures to reduce/prevent RSV virus in addition to high-titer RSV-IgG include RSV-Fab infusions and immunization to specific RSV proteins. Until these therapies materialize, high-risk atopics would best benefit from receiving transferred IgA, and IgG, specific RSV-antibodies from breast milk.

Natural history of atopic disease (the "atopic march")

Risk factors – As noted earlier, the "atopic march", if not modulated, will progress often in the high-risk infant and child from 1) atopic dermatitis and food allergy to allergic rhinitis and allergic asthma, 2) infectious to allergic asthma, and 3) food sensitization to aeroallergen sensitization.

Interventions – Secondary prevention measures could play a modulatory role in this "atopic march", as noted above. Aeroallergen, ETS, and pollution avoidance, as discussed above, should be utilized in this effort at prevention. Additionally, modulation may be possible pharmacologically. Recently, ketotifen administration to infants less than age 3 with atopic dermatitis appeared to reduce the prevalence of asthma onset over the subsequent 12 months from 42% to 14% in a randomized double-blind placebo-controlled study, with an effect seen predominately in those with serum IgE levels > 50 IU/ml (35). Present studies in Sweden and England [Early Treatment of the Atopic Child (ETAC)] are attempting to confirm these findings. The use of immunotherapy for allergic rhinitis in children has been recommended (36), but is far from proven, to prevent the progression of allergic rhinitis to allergic asthma.

Limitations of allergy prevention

Allergy prevention efforts have been limited by 1) only moderately sensitive and specific prediction

Table 8. Advantages and disadvantages of primary and secondary prevention of atopy

Primary prevention	Secondary prevention
Advantages	Advantages
Permits perinatal advice	Better capacity to predict atopic disease
Optimizes early parental commitment	More convincing to certain parents
Potential to prevent sensitization or early atopy	Prospective follow-up for atopy encouraged
Bridges atopy's "critical period"	Pediatricians' atopy quotient improves
Disadvantages	Disadvantages
Predictive markers possess low sensitivity	May miss "critical period" of sensitization
Involves many families not at real risk of atopy	Atopic disease may have developed
Minimal effective preventive efforts unknown	Usual medical care may not allow prospective follow-up
Costs, QOL, aeroallergen effectiveness undetermined	Costs, QOL, effectiveness undetermined

Table 9. Lobbying for international allergy awareness and prevention

A. Rationale	
•	Unrelenting increase in atopy and asthma
•	Increase in asthma morbidity and mortality despite pharmacologic advances
•	Occupational allergy rising
•	United States cost – \$6 billion annually for asthma
B. Community factors	
•	Poor public allergy education and awareness
•	Breast feeding not optimized
•	ETS and air pollution still high
•	High-risk atopic and low SES underserved
C. Identify high-risk atopics	
•	Future genetic markers
•	Atopic parentage and elevated cord blood IgE levels
•	Postnatal atopic markers
•	Low SES and ethnic clusters
•	High-risk occupations
D. Universal prevention strategy	
•	Promote lengthy breast feeding
•	Discourage early solid foods
•	Screen for simple atopic markers during well-baby visits
•	Recognize atopy early and advise or refer for prevention guidelines
•	Construct mite retardant homes
•	Campaign for ETS control/cessation
•	Stop pollution and pollutants
•	Institute atopic work safeguards
•	Screen pre-employment for atopy
•	Encourage support organizations
E. Individual high-risk prevention strategy	
•	Supplement/wean with hypoallergenic protein hydrolysate
•	Promote mite avoidance (encasings, bare floors)
•	Discourage indoor allergenic pets
•	Delay day care
•	Avoid atopic high-risk occupations
F. Future strategies	
•	Prevent RSV infections
•	Oral tolerance to aeroallergens
•	Modulate T cells (peptide antigens)
•	Modulate cytokines (monoclonal antibodies, antagonists)
•	Modulate atopic genes (science fiction?)

markers (4), 2) complexity and demands required in allergenic avoidance (4), 3) levels of compliance of caretaker and child (24, 37), 4) lack of societal understanding/commitment combined with increasing urbanization, and 5) inadequate resources/finances (Table 7) (38).

Advantages and disadvantages of primary and secondary prevention

A critical examination of both primary and secondary allergy prevention (Table 8) reveals relative advantages and disadvantages of each preventive stage. Both stages complement each other and should be invoked together to successfully counter the allergy epidemic facing the world today.

National (international) urgency for allergy prevention

The alarming increase in the prevalence and morbidity of most, if not all, atopic diseases, as particularly apparent with asthma, probably has arisen over the past two decades from the consequences of 1) urbanization (encouraging ornamental pollinating plants and grasses, and spewing pollution wantonly), 2) excessive ETS, 3) increased exposure to occupational allergens, 4) poorly ventilated homes with carpeting/wool blankets which encourage warmth/humidity leading to mite proliferation, 5) increased survival of critically ill neonates with respiratory disease, as well as other factors not yet identified. To confront this atopic maelstrom, a national and international consciousness directed towards allergy prevention must be developed. Otherwise, this atopic epidemic will become more pervasive, unmanageable and deadly. Measures deserving merit for development of this worldwide allergy consciousness are described in Table 9.

Future of allergy prevention

Future scientific advances which identify the genetic and immunologic basis of atopy more precisely will surely lead to monumental new strategies to prevent atopic disease. Some of these strategies are noted in Table 9. For the time being, in addition to the above proposed recommendations for allergy prevention, it would not hurt to have a bit of assistance from the friendly gods. In the interim, families should be provided with an Allergy Prevention Bill of Rights to protect them from the ravages of atopic disease. These rights could include the 1) right to be breast, not formula, fed, 2) right to live in dust-miteless homes, 3) right to be free from indoor pets, 4) right to be free from ETS, 5) right to breathe clean, not polluted, air, and 6) right to be screened for/advised of allergy prevention as part of child care.

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