



Prevention of Allergic Asthma with Allergen Avoidance Measures and the Role of Exposome

Gennaro D'Amato^{1,2} · Olga Patricia Monge Ortega^{3,4} · Isabella Annesi-Maesano⁵ · Maria D'Amato^{6,7}

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Abstract

Purpose of Review It is well known that combination of sensitization and exposure to inhaled environmental allergens is related to both the development and elicitation of symptoms of asthma and that avoidance of allergens would exert beneficial effects in the prevention and control of the disease. Other important factors include the relevance of other allergens, exposure to sensitizing agents also outside patient's home, exposure to irritants (like chemical air pollutants), and the involvement of the patient with a correct education. It is also likely that clinical phase of allergic airway disease and the degree of airways remodeling represent relevant factors for the clinical outcome of allergen avoidance procedure. We reviewed existing evidence on prevention of asthma through allergen avoidance.

Recent Findings The management of respiratory allergy is a complex strategy (including prevention, drugs, immunological, and educational interventions). In addition, it is difficult in real life to distinguish the efficacy of single interventions. However, a combined strategy is likely to produce clinical results.

Summary A combined strategy is likely to produce satisfactory management of asthma. Allergens are an important trigger factor for the development of symptoms of respiratory allergy, and avoidance measures are able to reduce allergen levels. It is likely that clinical phase of allergic airway disease and the degree of airways remodeling represents relevant factors for the clinical outcome of allergen avoidance procedures. Considering the management of respiratory allergy is a complex strategy; it is difficult in real life to distinguish the efficacy of single interventions. However, further studies better quantifying the effects of allergens are needed.

Keywords Respiratory allergy · Allergenic pollen · Climate change and allergy · Biodiversity and Allergy · Pollen allergy · Severe allergic asthma · Exposome and respiratory allergy · Thunderstorm asthma · Seasonal allergy

Abbreviations

AQI	Air quality index
Der f	Dermatophagoides farinae
Der p	Dermatophagoides pteronyssinus
ETS	Environmental tobacco smoke
CO	Carbon monoxide
Fel d	Felis domesticus
HEPA	High efficiency particulate air
HDM	House dust mite
HVAC	heating, ventilation, air conditioning systems
systems	
MERV	Moderate-efficiency filters
O3	Ozone
PM	Particulate matter
PRACs	Portable room air cleaners
SBZ	Sleep breathing zone
SO2	Sulfur dioxide
WFH	Whole house filtration

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✉ Gennaro D'Amato
gdamatomail@gmail.com

¹ Division of Respiratory and Allergic Diseases, Department of Chest Diseases High Speciality, A. Cardarelli Hospital, Napoli, Italy

² Medical School of Specialization in Respiratory Diseases, University of Naples Federico II, Napoli, Italy

³ Allergology Unit, San Juan de Dios Hospital, San José, Costa Rica

⁴ University of Costa Rica, San José, Costa Rica

⁵ EPAR Department, NIH (INSERM), Paris, France

⁶ First Division of Pneumology, High Specialty dei Colli, Hospital V. Monaldi, Napoli, Italy

⁷ University of Naples Federico II, Medical School, Napoli, Italy

Introduction

To draw attention to the need for better and more complete environmental exposure data for causal research, Wild introduced the concept of exposome [1]. The exposome encompasses life-course environmental exposures from preconception onwards. There are three overlapping domains within the exposome [2]. These are the following:

- 1) A general external environment including the urban environment, education, climate factors, social capital, and stress.
- 2) A specific external environment with specific contaminants, radiation, infections, lifestyle factors (e.g. tobacco, alcohol), diet, and physical activity.
- 3) An internal environment to include internal biological factors such as metabolic factors, hormones, gut microflora, inflammation, and oxidative stress.

It is well known that combination of sensitization and exposure to inhaled environmental allergens is related to both the development of asthma and elicitation of symptoms and that avoidance of allergens would exert beneficial effects in the prevention and control of asthma [3, 4].

It has been clearly shown that allergens are important trigger factors for the development of symptoms of respiratory allergy and that avoidance measures are able to reduce allergen levels [5]. It is likely that the clinical phase of allergic airway disease and the extent of airways remodeling represent relevant factors for the clinical outcome of allergen avoidance procedures [6]. Considering that the management of respiratory allergy involves a complex strategy, it is not easy to distinguish the efficacy of single interventions. However, a combined strategy can be useful to produce better clinical results.

It is now evident that the development of respiratory allergy depends on a complex interaction between genetic background and environmental factors. Among the latter, exposure to allergens and indoor and outdoor air pollution seem to be the more relevant [7]. It is also possible that changes induced by human activities, as well as the “westernized” lifestyle, play an important role in increasing the prevalence of allergic, IgE-mediated diseases in the general population [8]. On the other hand, it is now accepted that atopy, particularly in children, is the main risk factor for the development of bronchial asthma [9].

The peculiarity of modern indoor environments (insulation of doors/windows, reduced natural ventilation, upholstered furniture, central heating, etc.), in addition to

the current lifestyle (time spent prevalently indoors), increases the duration and intensity of exposure to indoor allergens such as mites, pets, and cockroach products [4, 10] as well as to indoor chemical agents. In this context, it has been clearly shown that exposure of sensitized subjects to allergens is a risk factor for development and exacerbations of allergic-atopic asthma [11, 12].

Some studies suggested that the effect of the environment on airways starts early. For instance, it has been shown that maternal smoking in pregnancy has a significant impact on lung function in the newborn [13, 14]. These observations indicate the importance of preventive or avoidance measures during pregnancy [15].

Indoor Allergen Avoidance in Pregnancy and Early Life (Primary Prevention)

In the last few years, an increasing interest has been devoted to the perinatal period and early infancy as critical time intervals for the subsequent development of respiratory allergy [16, 17, 18]. This has envisaged the possible role of reducing exposure to aeroallergens in these periods to prevent the development of allergic sensitization and bronchial asthma. Indeed, apart from exposure to tobacco smoke, the scientific evidence for the effects of environmental factors on the development of allergic sensitization and asthma is still controversial [19]. Effective primary preventive methods have been difficult to assess, and those currently suggested are questionable [20].

The optimal approach to study the effects of primary prevention should be a randomized intervention study, starting in pregnancy and involving many high-risk families. This type of study is complex, time-consuming, and expensive but crucial to establish the efficacy of such an approach to reduce the prevalence of respiratory allergies. Environmental interventions were generally able to significantly reduce allergen load (especially those of dust mites) [21]. On the contrary, although preliminary results are encouraging, no final conclusion on the clinical effect of allergen avoidance in reducing the risk of developing respiratory allergy can be drawn [22, 23].

It is not known how long these intervention measures should be continued, and how long the children should be followed up, but it is likely that a very long time would be necessary to obtain incontrovertible answers.

The environmental interventions to reduce the levels of indoor allergens, especially those produced by mites and pets, used in the primary prevention studies are the same that were

recommended in secondary and tertiary prevention. It is important to outline the role of the compliance of the parents receiving advice to reduce exposure to mite and pet allergens and to avoid passive smoking [24•, 25].

Mattresses and Bedding Materials

Beds are the most important source of mite allergens. Based on this background, the reduction of mite allergen exposure in the bedroom and bed is generally considered a primary target for avoidance measures. In clinical practice, it is often suggested to buy a new mattress for newborn babies. This recommendation relies on the assumption that new mattresses are free of allergen. A recent study by de Boer et al. [26] performed on newly bought mattresses demonstrated that only 15 of the 90 mattresses contained no detectable amount of the four tested allergens (Der p 1, Der f 1, Fel d 1, and Can f 1). The study also showed that new mattresses, wrapped in plastic, may still contain a substantial amount of these same allergens and does not substantiate the clinical-based recommendation for newborns. It is also suggested that regular vacuuming of new mattresses assists the removal of mite allergens. Additionally, new mattresses are rapidly infested by dust mites under favorable climate and housing conditions such as dampness [27].

It is usually accepted that the most effective avoidance measure is the use of mite-impermeable covers for the mattresses, pillows, and duvets [28, 29] in association with washing bedding materials at hot temperatures. The type of material used for encasements (plastic sheet, polyurethane, non-woven tissues, and microfiber covers) represents an important variable. In this regard, Mahakittikun et al. [30] performed a detailed laboratory assessment (heat escape method, Siriraj chamber method, stereomicroscopy, scanning electron microscopy, and enzyme-linked immunosorbent assay) to establish the efficiency of encasement materials against house dust mites and their allergens. Only encasements with a pore size of 2–10 μm (mean 6 μm), such as tightly woven microfiber covers, could completely prevent the passage of mites and mite-derived materials while still retaining a good level of comfort and air permeability [31]. Encasements are clearly able to reduce the amount of mite allergens. Some previous [32] and a recent [33] meta-analyses have confirmed that bedding encasement might be an effective avoidance procedure in some patients with asthma.

Indoor Air Control

Control of Humidity

The control of indoor humidity (<45%) is an important measure to reduce mite growth. However, evidence that a

reduction in indoor humidity induces a concomitant reduction in humidity in mite microhabitats is still lacking [21, 34].

Humidity is a very important factor of HDM (house dust mite) growth and survival. Raised temperature can cause an increase in humidity, possibly influencing the growth and survival of HDMs. This effect could occur in temperate zones, where the increase in relative humidity during the whole year can augment the level and persistence of exposure. Humidity is a great limiting factor for HDM growth and has a profound influence on their reproduction. Mites absorb vital moisture from the air through their supra coxal glands and exoskeletons, requiring high air humidity to prevent excessive water loss. Critical air humidity differs among mite species, for instance, 47–50% for *D. farinae*, 60–65% for *D. pteronyssinus*, and 74–80% for *B. tropicalis* [35].

Increased house humidity has been related with increased prevalence of allergic and respiratory symptoms of asthma, as well as IgE levels, and is a well-recognized risk factor for HDM allergy. A raise in humidity in indoor air can affect the growth of HDM and allergen production; thereby, factors modifying the control of the indoor environment such as ventilation systems, air conditioning, and building materials will be critical in facilitating HDM exposure and sensitization. Building strategies have varied to make tighter and smaller homes, often resulting in higher indoor humidity and reduced indoor air quality. Patients living in households without air conditioning are at increased risk of mold sensitization and polysensitization. Air conditioning can also increase indoor dampness by leakage of water in walls as well as by creating condensation in those and in the windows. The overall results of moisture and water accumulation may lead to HDM and mold growth [35].

Some studies have suggested that dehumidifiers in the basement and air conditioners may play an important role in controlling mite growth in temperate climate. Nevertheless, the outcomes of such measures are marginal, and their clinical efficacy is too controversial to make strong recommendations [36].

Air Filtering

Air filtration is frequently suggested as a part of environmental control practices for patients with allergic respiratory disease. Residential air filtration can be provided by WHF (whole house filtration) via the home's HVAC system (heating, ventilation, air conditioning systems), PRACs (portable room air cleaners), or a combination of both. Appliances to filter the SBZ (sleep breathing zone) also exist. HVAC systems may create a reservoir for triggers if they are not well-maintained. Economic, low-efficiency HVAC filters offer no better particle removal than no filter. WHF with high-efficiency HVAC filtration is shown to be more effective in particulate reduction than individual

HEPA (high-efficiency particulate air) PRACs. The combining HVAC maintenance with a disposable high-efficiency MERV 12 HVAC filter has shown clinical benefit of WHF in asthma. A study of HEPA PRACs trended toward clinical benefit but their effectiveness is limited to a single room and not the whole dwelling. Several—placed in various rooms—are needed to approach the benefit of high-efficiency WHF. Ionic electrostatic room air cleaners produce little or no benefit compared with WHF or HEPA PRACs. Ionic appliances produce ozone and respiratory irritant and caused an increase in submicrometer particulates. SBZ filtration was found to be effective in clinical studies. The best and most cost-effective approach may be to consider “combination filtration” using high-efficiency WHF with PRAC or breathing zone filtration in the bedroom [37].

The principal requirements for an optimal air-filtering system are as follows: low resistance to airflow, cleaning efficiency, low or no need for maintenance interventions, and long life [38].

Fisk et al. [39] used a mass-balance model to estimate reductions in the indoor concentrations for a range of particle sizes during utilization of various air filtration systems, including both HVAC (heating, ventilation, air conditioning) systems and PRACs (portable room air cleaners). They concluded that for cat and dust mite allergen—predominantly found in particles with a diameter of several micrometers—the predicted reductions in indoor mass concentrations (mass per unit air volume) ranged from less than 20% for the typical inexpensive (fiber glass-woven) furnace filter (no American Society of Heating, Refrigerating and Air-Conditioning Engineers (ASHRAE) rating) to 60% for a HEPA filter. Moderate-efficiency filters (MERV 11–12) worked well for the larger diameter particles. Increasing filter efficiencies above ASHRAE 65 to 85% (MERV 11–13) to a HEPA filter did not reduce indoor concentrations significantly. For ETS (environmental tobacco smoke) fine-mode particles (<PM_{2.5}), 80% decreases in indoor concentrations were attainable with filter efficiencies in the same range (MERV 11–13) and flow rates. Increasing the filter efficiency above ASHRAE 85% (MERV 13) to HEPA resulted in only modest predicted incremental decreases in indoor concentrations of these smaller particles. Filters with an efficiency rating of ASHRAE 45% (MERV 9) or lower were not found to be effective for reducing indoor concentrations of these smaller particles. In addition, in modeling for the PRACs, they found increasing airflow exchange rates to be more important than increasing filter efficiencies to HEPA. This author reflects that the three critical attributes of an air filter are the balance of efficiency, holding capacity of the filter as it loads with dust, and adequate airflow through the filter throughout its expected life.

Anti-Mite Interventions

Chemical Agents

Over the last 30 years, a variety of chemicals has been tested for their ability to kill mites in culture.

It is important to outline that mites are not insects and that many excellent insecticides do not kill mites at the concentration that can be used in houses. Although many agents demonstrate optimal in vitro activity, their efficacy in real life depends upon other factors such as method and time of application, type of formulation (liquid, moist powder, foam, spray, etc.), local conditions (e.g., type and thickness of carpets), and effectiveness of vacuum cleaning in removing dead mites and their products from reservoirs after their use.

There is no complete agreement about results of clinical studies testing these products. In fact, some authors demonstrated positive benefits in controlling mite populations and, consequently, clinical symptoms in allergic patients, but other studies failed to confirm these positive effects [16•]. Most studies of acaricides or allergen-denaturing agents suggest that applications every 2–3 months are needed to prevent mite re-infestation [40].

Vacuum Cleaners

The use of vacuum cleaner is useful to reduce the amount of allergens of *Dermatophagoides* in the reservoir but the contemporaneous use of other preventive measures is recommended for effective reduction of allergen content in furnishings [41].

The major problem with vacuum cleaners is that, independently from the potency of the apparatus, they are not able to completely remove live *Dermatophagoides* from surfaces (carpets and other surfaces); additionally, they even allow debris to accumulate. There are critical aspects in carpet cleaning: in particular if the cleaner can remove dust from the carpet and how much allergen/dust becomes airborne when the cleaner is in use.

Gore et al. [42] showed a 3 to 5 fold increase in personal cat allergen exposure while using both high-efficiency new vacuum cleaners and older vacuum cleaners including a water-activated device. The evaluation of personal exposure to allergen was carried out using nasal air samplers [43] for 15 min. This finding is probably due to high concentrations of cat allergens in dust reservoirs (such as carpets, soft furnishing, mattresses, and also wall surfaces) of houses containing a cat.

Anti-Mite Measures in Pets

Conflicting opinions still exist in literature about the efficacy of prevention strategies to avoid exposure to the allergens of domestic animals (need ref. here), particularly cats and dogs.

Many pet-sensitized patients, particularly children, refuse to give up their animals [44]. Other patients, despite the obvious source of their symptoms, are often unwilling to recognize the correlation between pet-ownership and clinical symptoms and consequently refuse to remove their cats. Finally, it has been shown that parents of cat allergic children (about 55%) deny that their child's symptoms are worsened by the pet's presence [44]. These are some of the reasons why, in the majority of cases, the reduction of pet allergens must be carried out with the animal standing at home. An intensive avoidance procedure (replacing furniture and blankets, vigorous vacuum cleaning, and using air filtration systems) carried out after cat/dog removal, can significantly reduce the levels of Fel d 1 and Can f 1 [40]. Many studies have evidence that the majority of domestic environments (and public places) where a cat/dog has never been kept may still contain significant amounts of Fel d 1 and Can f 1 [40]. Some authors have consistently demonstrated that the clothes of cat owners represent the main source for the dispersal of cat allergens in cat-free environments [45].

These considerations suggest that the removal of cat proteins from the clothes of cat owners may be an important approach for the prevention of dispersal of these allergens in animal-free environments [46].

Based on these premises, we designed a project to evaluate the efficacy of different methods of cleaning (with and without the use of water) materials passively contaminated by contact with cats. We demonstrated that Fel d 1 can be completely removed from contaminated cotton webs by simply washing them in water [47]. Also, we recently evaluated the efficacy of commercial dry cleaning that is commonly used in industrialized countries, using the same study design and a different type of material (wool). Dry cleaning was able to remove large amounts of Fel d 1 from contaminated wool fabrics but did not completely abolish cat allergen contamination [48•]. Further, *Fel d 1* contamination of three control (previously non-exposed) wool rectangles after dry cleaning suggested that cat allergens can be transferred from other clothes during the dry cleaning process [48•].

It was suggested that washing domestic animals can be an efficient strategy to remove allergens from the body surface [5]. Unfortunately, the amount of pet allergens rapidly increases after washing and returns to previous level within a few days. Therefore, in order to achieve a satisfactory reduction of the allergen level, the dog should be washed once, or better two times a week [49•].

The aerodynamic properties of cat/dog allergens justify the use of air filtration systems in indoor environments where these pets are present [50, 51]. Thus, long term use of HEPA-equipped air cleaners may be useful to remove large amounts of airborne particles carrying dog and cat allergens [36].

The use of a common furniture polish on either dusty surfaces or cleaning cloths during dusting was demonstrated to

be useful in reducing both dust and cat allergens (Der p 1 and Fel d 1) dispersal [52]. However, a recent study demonstrated that the common recommended intervention measures (cleaning all internal surfaces, removal of textiles, use of encasements, etc.) did not reduce the amounts of airborne cat allergen [53].

Outdoor Air Pollution and Allergens

Climate change may affect air pollutant levels in several ways: regional weather (e.g., changes of wind patterns, amount and intensity of precipitation, and increase of temperature), anthropogenic emissions, and the severity and frequency of air pollution episodes. For example, an increase of energy demand for space heating or cooling can lead to enhancement of the urban heat island effect, which may increase some secondary pollutants (i.e., ozone) and indirectly lead to increased natural sources of air pollutant emissions, such as decomposition of vegetation, soil erosion, and wilderness [54].

Air pollution can increase oxidative stress, and prenatal or postnatal stress and pollutants can have synergistic harmful effects on lung function.

Cigarette smoking can modify the effect of air pollution on asthma in adults because current or former smokers appear to be more prone to incident asthma related to outdoor pollutants than non-smokers. Second-hand smoke increases the risk of childhood asthma and can thus worsen the effects of air pollution in this disease. Concomitant exposure to air pollutants and aeroallergens can enhance airway inflammation and lead to asthma exacerbations. Scientific studies in adults have demonstrated enhanced allergen-induced airway inflammation in patients exposed to nitric oxide and ozone [55].

Measures to Improve Outdoor Air Quality

A significant amount of research still needs to be conducted to better understand the health impact of air pollution. Future investigations should use a multidisciplinary approach incorporating biologic, genetic, epidemiologic, and clinical methods. However, public health approaches to decrease the general public's exposure to air pollution should take into consideration the following goals: to reduce the use of fossil fuels and control vehicle emissions; reduce private traffic in towns and improve public transportation, which also favors pedestrian traffic; and to plant trees of non-allergenic species in cities. Moreover, increasing the antioxidant defenses of the human airways by eating antioxidant foods should be encouraged [56].

The detrimental effects of ambient air pollution can be reduced by decreasing the time spent on outdoor activities, and the level of activity when the air quality index (AQI) is higher than a specified level. The AQI is a number used by government agencies to communicate to the public the current

degree of air pollution or how polluted it is forecasted to become. It is calculated from four major air pollutants: ground level ozone (O₃), particle pollution, carbon monoxide (CO), and sulfur dioxide (SO₂) [57].

Wearing personal protective equipment (N95 mask or equivalent) might be useful to reduce or eliminate detrimental effect of ambient air pollutants. Using a nose mask in haze environment can help to prevent adverse effects from vehicular pollution [58].

The Public Health England shows some interventions and approaches to improve outdoor air quality and public health [59] and these are as follows:

- 1) Implement specific interventions to address specific local sources or problems identified through assessments by local authorities.
- 2) Execute according to the priorities the interventions that prevent or reduce emissions on those that address pollution once it has occurred.
- 3) Decreasing the use of pollution sources in populated areas. Interventions in urban areas may target emissions from road vehicles (promotion of public transport, cycling, use of electric vehicles) or emissions from wood-burners (using cleaner fuels or replacing old appliances).
- 4) Systematically evaluating the interventions. Evaluation should be embedded in the design and costing of all future interventions, from their outset, to systematically get evidence to inform best practice in the future.

Conclusions

It has been shown that allergens are important risk factors for the development of respiratory symptoms, but the clinical results deriving from avoidance studies remain conflicting.

A successful approach to prevent symptoms of allergy requires avoiding exposure to allergens. Other factors of importance include the involvement of the patient with an educational approach, and to reduce exposure to sensitizing agents in both indoor and outdoor settings.

In our opinion, the clinical phase of allergic airway disease and the degree of bronchial (and also nasal) remodeling represent relevant factors for the clinical success of allergen avoidance interventions. Since the management of respiratory allergy is a complex strategy (including medication, prevention, immunological, and educational interventions), it is difficult in real life to distinguish the efficacy of a single intervention in comparison to the others. A combined strategy is likely to produce better clinical results.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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