Evidence-based effectiveness of indoor environmental control for the treatment of allergic asthma

FOCUS ON HOUSE DUST MITE ALLERGY

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The studies described in the thesis were performed at the Section of Allergology and Clinical Immunology, Department of Internal Medicine, Erasmus Medical Center Rotterdam, The Netherlands

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Evidence Based Effectiveness of Indoor Environmental Control for the Treatment of Allergic Asthma: Focus on house dust mite allergy

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The important thing in science is not so much to obtain new facts as to discover new ways of thinking about them.

Sir William Henry Bragg (1862 -1942)

CONTENTS

CHAPTER 1

Introduction

This thesis discusses the effectiveness of house dust mite allergen control in the treatment of allergic asthma. Allergic asthma is a major public health problem affecting several million people worldwide, and its prevalence continues to increase [1,2]. The progression of allergic asthma primarily involves allergic sensitization to house dust mites [3]. Common therapies for the treatment of allergic asthma include allergen avoidance or tertiary prevention, pharmacotherapy, and immunotherapy [1]. However, the clinical effectiveness of avoiding house dust mite allergen exposure is considered a controversial subject [4]. Additionally, clinical evidences of the benefits of avoiding pet allergen exposure remain elusive [5]. The absence of considerable evidences necessitate an explanation, since the allergen avoidance therapy was introduced as the cornerstone of allergy treatment [6]. Multiple issues play a complex and interactive role in associating clinical outcomes with the control of allergen exposure [7]. Prior to discussing the points of the debate on clinical effectiveness of house dust mite allergen avoidance, we first introduce the mono-disciplinary topics that are associated with this subject. This introduction consecutively describes in brief the problem of allergic asthma, the biology of house dust mites, indoor allergen exposure, the environmental control of exposure, and the concept of effectiveness assessment using systematic reviews. After discussing the debated points on house dust mite allergen avoidance, we present the aim of this thesis.

Asthma

Asthma is a chronic inflammatory disorder of the lower conducting airways [8]. The airways are hyper-responsive to a variety of triggers, allergens being one of them [8]. The inflammation results in respiratory symptoms such as wheezing, cough, shortness of breath, and sleep disruption [8]. An exacerbation is an acute situation marked by severe shortness of breath, necessitating a temporary increase in pharmacological treatment [9]. The Global Initiative for Asthma (GINA) classifies the severity of asthma by the level of treatment required to control symptoms and exacerbations [10]. Mild asthma is controlled by the use of a low dose inhaled corticosteroids (ICS) (level 1 and 2), whereas severe asthma requires a higher dose of ICS, long-acting beta$_2$-agonist, and subsequently, a biological add-on treatment [11]. In asthma, a phenotype (a set of observable characteristics) refers to a specific subgroup of asthma that requires a treatment different from that provided to another subgroup [12]. Asthma phenotypes have been defined in relation to clinical characteristics such as early-onset allergic, late-onset eosinophilic, exercise-induced, obesity-related, and neutrophilic asthma [12]. Environmental control of allergen exposure aims to treat the allergic phenotype of asthma.

IgE-mediated allergy

An allergy is an extreme reaction of the immune system to the introduction of a previously

encountered allergen in the human body [13]. In respiratory allergy, the allergen is introduced by inhalation, resulting in inflammatory symptoms in the exposed respiratory tract. The immune reaction in respiratory allergy is defined as an IgE-mediated reaction [14]. In susceptible subjects, introduction of allergens to and uptake by the respiratory tract may lead to subsequent uptake by the antigen presenting cells [15]. This is illustrated in Figure 1. Subsequently, the interaction with T-helper 2 cells leads to the production of IgE antibodies by B-cells [16]. Crosslinking of two IgE molecules bound to mast cells by an allergen leads to mediator release while disarming the antigen [17]. While histamine is the most important mediator in the acute phase of the allergic reaction, other mediators, such as cytokines and chemokines, are responsible for the late or delayed [that is, more chronic] phase [14]. The delayed phase is characterised by the activation of eosinophils and the involvement of T lymphocytes and Th2 cytokines, which play a crucial role in asthma [16]. The multiple mediators that are released by the mast cells activate the process of inflammation [14]. House dust mite allergens are a primary causative agent of IgE-mediated allergy [18]. We proceed to introducing their biology in the next paragraph.

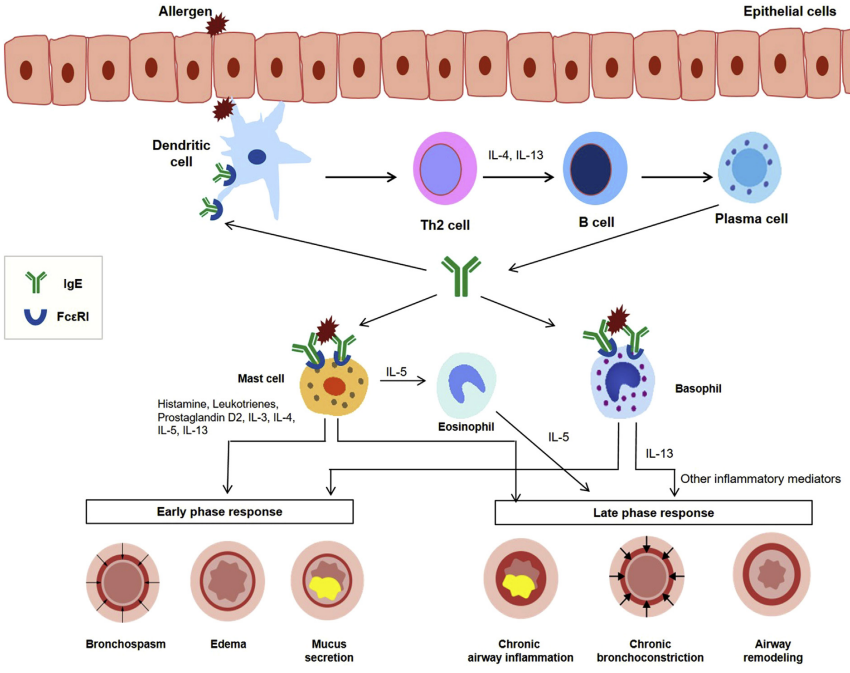

Figure 1. IgE-mediated allergic reaction.
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Biology of house dust mites

House dust mites are small arthropods (<0.5 mm) belonging to the family Pyroglyphidae [19]. The species most commonly detected in domestic environments worldwide include *Dermatophagoides pteronyssinus, Dermatophagoides farinae, Euroglyphus maynei,* and *Blomia tropicalis* [20]. House dust mites are primarily found in domestic textiles such as mattresses, carpets, upholstery, and soft toys [19]. They are cold-blooded, requiring an optimal temperature of 20 to 25 °C for development [21]; beyond this range, their development is slower. The optimal temperature range for humans [22] is close to the range required for the development of house dust mites. Therefore, the indoor thermal climate is not considered a long-term limiting factor for house dust mites. House dust mites are rapidly eliminated at higher temperatures, and tolerate a temperature of 60 °C only for ten minutes [21]. Conversely, house dust mites can survive in freezing temperatures (-20 °C) for 24 hours [21].

House dust mites contain 70 to 75% water in their body [21]. The water that is lost by excretion, defecation, secretion, reproduction, and evaporation needs to be replaced [23,24], preferably with water from sources other than metabolic water and the water in food [23]. When the absolute humidity of the ambient air is above a specific level, the water uptake is equal to or greater than the loss of water, and house dust mites can easily grow [23]. This specific limiting level is defined for the critical equilibrium activity (CEA) [25], and expressed by the relative humidity. When the relative humidity surrounding the house dust mite is below the CEA, they suffer dehydration and their survival levels reduce [23]. However, their survival is supported by short durations of daily peak humidity levels above the CEA [26].

The life cycle of house dust mites consists of six stages (egg, pre-larva, larva, protonymph, tritonymph, and adult), spanning approximately 15 days at 35 °C to 122 days at 16 °C [19]. During the last four stages, there is an active period followed by a quiescent period [19]. The quiescent period, represented by the protonymph, can last long, allowing a population to resist unfavourable climatic or nutritional conditions for several months [20]. Organs for oxygen and carbon dioxide exchange have not been detected in house dust mites [23]. There is limited information on their oxygen consumption [27], and it is not denoted as a limiting factor.

Amongst the environmental factors, the relative humidity in the niche is considered a limiting factor for the long-term control of house dust mite development [19]. In areas with a heating season, a combination of environmental means is required to lower the relative humidity in the niche [28]. This concurrent approach involves the intervention of interacting factors such as indoor heating, thermal insulation, the production of humidity, and indoor air ventilation [28].

The faecal pellets of the house dust mite are the most important source of allergens [20]. Mite allergens are classified based on their individual allergen components. The

group 1, 2, and 23 allergens are immunodominant, displaying the highest levels of reactivity in allergenicity assessments [20]. Group 1 and 2 allergens are proteases that increase the permeability of the respiratory mucosa [21], thereby inducing allergic inflammation with ease.

Indoor allergen exposure

House dust mites produce small spherical faecal pellets with a mean diameter of 22 μm (range 10 to 40 μm) [29]. With time, the wrapped faeces partially degrade into smaller fragments (diameter>0.5 μm) [30]. House dust mite allergens are released from textiles due to human activity [29]. Other indoor allergens amongst others are produced by cats, dogs (size<2 μm), and cockroaches (size>10 μm) [29,31,32]. While cat allergens are released from their fur, the allergen from dogs is detected in their saliva and urine [33]. Cat allergens are also found in buildings without cats, and are possibly introduced from the clothes of cat owners [34]. Cockroach allergens are primarily detected in their faecal products [32].

Methods have been developed to measure the indoor allergen exposure [35]. In a biochemical assay, the allergens bind to an antibody, and are consequently linked to an enzyme [36]. The enzyme produces a detectable signal that serves as a measure for the antigen concentration [36]. By sampling the house dust from a textile (load) or from the indoor air [airborne], the allergen concentration can be assessed. Measurement of the airborne allergen concentration requires a sensitive assay as the levels of airborne dust are very low [35].

Exposure to house dust mite allergen vary based on location and time [20]. Early investigations revealed that exposure to airborne allergens is characterised by a peak level or emission, followed by the settlement of the allergens [37]. A long-existing paradigm states that the contribution of house dust mite allergens to airway diseases is associated with the type of bedding used [6]. In a later rostrum, Tovey and Marks [7] advocated that this paradigm is considerably simple to account for the significant variation in house dust mite aeroallergen exposure. Moreover, in two pilot studies by Tovey et al. [38,39], they observed that bedding materials were not the primary source of house dust mite aeroallergen exposure. In these two pilots, exposure during (public) transport was the most significant [38,39].

Controlling indoor environmental exposure

Environmental sciences provide methods and approaches for describing exposure, and strategies and policies for controlling exposure. These strategies and policies can also be applied to issues related to house dust mite aeroallergen exposure.

In the environmental domain, engineering sciences describe pollution and noise problems in terms of a source, a transmission path, and a receiver [40]. Control measures may involve altering any one or all of these elements [40]. In case of house dust mite allergy,

we can consider a source (emission of allergen from a textile), a transmission path (airborne exposure), and a receiver (inhalation of allergen by the patient) in a chain spanning from a humid microenvironment to the appearance asthmatic symptoms (Figure 2).

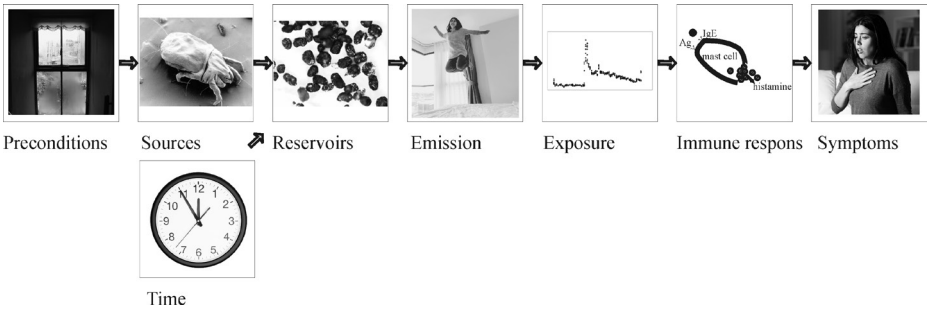

Figure 2. Chain of events leading to dust mite-related asthmatic symptoms starting from a humid indoor environment.
Window condensation: By Daniel Clauzier - Own work, CC BY 3.0, https://commons.wikimedia.org/w/index.php?curid=4531675
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Multiple environmental strategies for controlling house dust mite allergen exposure have been defined in the twentieth century. Total avoidance aims to create an indoor environment completely free of living and dead house dust mites as well as their faecal products [19]. An alternative for this strategy is to remove patients temporarily to a mite-free environment, such as in a hospital [41] or to an alpine mite-free environment [42]. Source-based approaches result in exposure-based control [43] and concurrent bedroom interventions [24]. In exposure-based control, the choice of intervention is based on the primary assessment of the actual exposure in the domestic environment [43]. Concurrent bedroom interventions are strategies of combining priori defined bedroom barriers [24]. Both textile-based strategies employ methods aimed at killing mites (hot washing at 60 °C and use of tannic acid or biological products for killing mites, such as neem-oil) and preventing the release of allergens from the bedding materials (using a mite-impermeable cover or removal of upholstery). All of these products have been tested for clinical efficacy in randomized trials, in varying combinations [4]. The receiver-based strategy of air purification [44] aims at altering the element of the airborne exposure, often by using a high-efficiency particulate air (HEPA) filter, with a diameter of 0.3 μm, capturing at least 85% of airborne particles, including those containing mite allergens. HEPA filters are

usually utilized in ventilation devices, both mobile as well as the mechanical ventilation in a home [44]. A specific application involves the purification of air directly above the pillow, defined as the nocturnal laminar airflow [45]. Another receiver-based approach could be the use of a mouth cap, as studied in the treatment of rhinitis using nasal filters [46]. A particular strategy amongst the former is humidity control [47]. This strategy aims to control the house dust mite population [47], however not primary eliminating the primary allergen exposure. As the faeces of dust mites remain allergenic for years [48], in principle, the elimination of house dust mites does not yet support the environmental treatment of allergic asthma. Therefore, in tertiary prevention, combining humidity control with a textile-based approach should always be considered.

Environmental policies for controlling pollution aim for total elimination if possible. The ALARA-principle (As Low As Reasonably Achievable) is commonly used in environment management [49]. Neutrality is another policy, similar to that used in the global warming agenda [50]. Neutrality aims to bring the current exposure to a standstill. The textile-based strategies of exposure-based control and concurrent interventions as well as air purification adopt a certain aspects of the ALARA-principle. A sojourn to an alpine environment aims for the total avoidance of pollutants.

The environmental control of exposure aims to realize clinical benefits for the patient. In the following paragraph, we introduce the concept for the assessment of clinical effectiveness at the highest level of evidence.

Evidence-based effectiveness of interventions and Cochrane reviews

Meta-analysis refers to the generation of results from individual studies, gathering robust information on the effectiveness with a high power at the highest level of evidence [51]. Cochrane reviews are considered the gold standard; they use explicit, systematic methods that are selected with an aim of minimizing bias, thereby providing more reliable findings from which conclusions can be drawn and decisions can be made [51]. Therefore, Cochrane reviews offer a strong starting point for the evidence-based question of the effectiveness of environmental interventions, such as house dust mite allergen control. Currently, four Cochrane reviews report the effectiveness of environmental means for the treatment of allergic asthma. In a review by Campbell et al. [52] the efficacy of using feather bedding was investigated. The trials sampled by Campbell did not fulfil the inclusion criteria. Gøtzsche and Johansen [4] reviewed the control of house dust mite allergen exposure in 55 trials. As stated, they were unable to demonstrate any clinical benefit from measures designed to reduce house dust mite allergen exposure. Kilburn et al. [5] studied the effectiveness of pet control. In this meta-analysis, the available trials were significantly limited for drawing conclusions. Singh et al. [53] provided limited evidence on the use of a mechanical ventilation heat recovery system. Overall, at the highest level of evidence, the environmental control of indoor allergen exposure as a treatment method for asthma cannot be recommended.

From debate to impasse

Debates are crucial for scientific developments [54]. A scientific debate is a dispute with contending knowledge claims, extending over a longer period, and dividing scientific groups [55]. In case of the question on allergen avoidance, the first randomized trials investigating extensive measures elaborately reported the benefits of treating allergic asthma [56]. At the end of the nineties, Gøtzsche [57] published his first meta-analysis on house dust mite allergen control and concluded that these methods "seem to be ineffective and cannot be recommended". During those years, the meta-analysis by Gøtzsche et al. received multiple comments [58-60]. The majority of comments were rejected by Gøtzsche as "none of the correspondents have provided data to the contrary" (at the same level of evidence) [61]. New randomized trials were introduced that did not alter the conclusions by Gøtzsche et al. [4,57,62]. Therefore, the debate on allergen avoidance is characterised by two scientific claims. The claim of no evidence by Gøtzsche dates to 1998. After the introduction of Gøtzsche's meta-analysis in 1998, no new claims were introduced at the same level of evidence. Concurrently, allergists in particular still believe that environmental means are of importance [63]. The debate on effectiveness of house dust mite allergen control reached an impasse.

Asthmatic patients and avoidance

The impasse on the effectiveness of allergen control is well-reflected in guidelines. The Global Initiative for Asthma (GINA) does not recommend allergen avoidance as a general therapy in asthma [64]. Particularly, the evidence for single measures is lacking. The World Allergy Organization concluded that the "Complete avoidance of offending allergens usually leads to an improvement of symptoms" [1]. On the basis of individual studies [66-68], the American Academy of Allergy, Asthma, and Immunology recommends minimizing the exposure to dust mite allergens in addition to avoiding other relevant allergens, to reduce the risk of developing symptoms [69].

The impasse predominantly affects the Dutch patients' practice. While scientific evidence is lacking and environmental means are not reimbursed, Dutch physicians still recommend home-related allergen control to the patients. The Lung Foundation Netherlands also recommends controlling exposure for patients who tested positive for house dust mite allergens (https://www.longfonds.nl/saneren). Dutch respiratory nurses are assigned to counsel patients on the treatment of the indoor environment. In the Netherlands, total control remains the starting point of such counsel [70]. However, long-term total control is barely achievable [56]. Asthmatic patients urge for access to updated evidence-based knowledge on possible clinical benefits of environmental means as well as means of exploring new environmental strategies.

Restarting the debate?

The impasse on the effectiveness of house dust mite allergen control is thus far dominated by the extensive Cochrane review by Gøtzsche and Johansen [4]. This meta-analysis is characterised by the simple linear combination of results from selected trials on avoidance, in an apparently fixed-effects model. However, the simple linear combination is contrasting to the variability in asthma [8], the significant variation in allergen exposure [39], and the complexity of exposure control [24]. A quick look at the data behind the meta-analysis by Gøtzsche and Johansen [4] reveals significant issues at times. For instance, the treatment group, as reported by Dharmage et al. [71], exhibited a median asthma symptom score of zero at baseline. While Burr et al. [72] provided the treated patients with only a mattress encasing, the intervention by Rijssenbeek et al. [73] (including encasings, hot washing of sheets, and smooth bedroom floors) could be considered to have facilitated total avoidance within the bedroom. In terms of avoidance, the difference was starkly contrasting.

An inadequately discussed topic is whether the effectiveness of house dust mite allergen control varies for different asthmatic patients, or for differences in interventions, or differences in their homes. Possibly, results obtained from the investigation of these questions could restart the debate.

Goal

This thesis aims to systematically review whether patients with allergic asthma benefit from environmental means of avoidance, with regard to the type of patient and differences in exposure, the strategy of the choice, and the types of interventions, with a focus on house dust mite-related asthma. Specific topics facilitate the exploration of oxygen content as a factor limiting dust mite survival and the description of personalized allergen exposure.

To study the influence of the variation in patients, their exposure, and the differences in interventions, the following sub-aims were defined:

1. To update and extend the existing Cochrane review by Gøtzsche and Johansen [4], with a focus on baseline asthma outcomes and allergen exposures.
2. To reintroduce previously defined strategies for mite allergen control and discuss their importance in the debate on clinical effectiveness, including future investigations.
3. To continue the meta-analysis by Gøtzsche and Johansen [4] by proposing hypotheses on the effectiveness of varying bedding interventions limited to mite-impermeable covers.
4. To update the existing systematic review by McDonald et al. [44] by reviewing the clinical effectiveness of the air purification strategy.
5. To systematically review the relationship between mite allergen exposure and altitudinal characteristics in Europe using existing data subsets.

6. To examine how house dust mite aeroallergen exposure levels have been reported historically, and subsequently, investigate the most effective methods of reportage.

Outline of the thesis

This thesis reports the subject of clinical effectiveness (chapter two to five) and the topic of exposure (chapter six and seven). Chapter two details the asthmatic patients and the condition of their domestic environment on which the current evidence is based. Baseline characteristics from randomized trials are described for the house dust mite allergen load from mattresses as well as the most reported asthma outcomes. In chapter three, we reintroduce the strategies of house dust mite avoidance. The results by Gøtzsche and Johansen [4] are sub-grouped into the specific strategies and discussed. A specific product used in house dust mite allergen avoidance is the mite-impermeable cover that is used to wrap bedding equipment. In chapter four, we propose hypotheses on the effectiveness of using mite-impermeable covers, when executed according to the concurrent bedroom interventions, as defined by Colloff [24]. The clinical effectiveness of air purification for the treatment of home-related allergic asthma [44] is updated in chapter five. This strategy involves the use of HEPA filters in mobile devices as well as the nocturnal laminar airflow for the treatment of home-related allergic asthma (house dust mite, dog, cat, and cockroach allergies). The last two chapters report the subject of exposure. In chapter six the relationship between mite allergen exposure and altitudinal characteristics in Europe is studied using a meta-analysis. The environmental characteristics implicate the outdoor temperature in January as a substitute for humidity and air pressure, and to study the possible influence of the reduced oxygen levels at high altitudes on the survival of house dust mites. Chapter seven discusses the description of house dust mite aeroallergen measurement results in bedrooms. Fluctuating aeroallergen measurements are commonly summarized using the mean. We introduced the peak exposure as an additional characteristic for denoting house dust mite aeroallergen exposure. The results presented in chapter two to six are summarized and discussed in chapter seven. A summary is also presented in Dutch.

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CHAPTER 2

The baseline characteristics in dust mite allergen avoidance trials

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A meta-analysis of baseline characteristics in trials on mite allergen avoidance in asthmatics: room for improvement. Clinical and Translational Allergy. 2020;10(2):1-12.

ABSTRACT

Background

Evidence regarding the clinical effectiveness of mite allergen avoidance for the treatment of asthma is lacking. In previous meta-analyses on mite allergen control, the baseline data were not discussed in detail. This study updates and extends the existing Cochrane review by Gøtzsche and Johansen (Cochrane Database of Systematic Reviews, 2008, Art. No: CD001187), with a focus on baseline asthma outcomes and allergen exposures.

Methods

We used the existing trials in the original Cochrane review and included newly published studies. The baseline data for the mite allergen load from the mattress, the standardized asthma symptom score (ASS), the forced expiratory volume in 1 s percentage of predicted (FEV_1 %pred.), and the histamine provocative concentration causing a 20% drop in FEV_1 (PC_{20}) were extracted. First, the mean values of the outcomes were calculated. The influence of the mite allergen load was examined with a random-effect meta-regression using the metafor package in R.

Results

Forty-five trials were included; 39 trials reported strategies for concurrent bedroom interventions, and 6 trails reported strategies for air purification. The mite allergen load ranged from 0.44 to 24.83 μg/g dust, with a mean of 9.86 μg/g dust (95% CI 5.66 to 14.05 μg/g dust, I^2 = 99.8%). All health outcomes showed considerable heterogeneity (standardized ASS mean: 0.13, 95% CI 0.08 to 0.18, I^2 = 99.9%; FEV_1 %pred. mean: 85.3%, 95% CI 80.5 to 90.1%, I^2 = 95.8%; PC_{20} mean: 1.69 mg/mL, 95% CI 0.86 to 2.52 mg/mL, I^2 = 95.6%). The covariate mite allergen load did not significantly influence health outcomes.

Conclusion

This meta-analysis shows that mite avoidance studies are characterized by the inclusion of patients with rather mild to moderate asthma and with varying and sometimes negligible levels of allergen exposure. Future studies should focus on patients with severe asthma and increased levels of allergen exposure.

INTRODUCTION

House dust mite-allergic asthma is a prevalent disorder of the lower airways that affects hundreds of millions of people worldwide [1, 2]. The immediate allergic reaction to mites [3] suggests that controlling exposure to the antigen could be an appropriate first-line therapy for the treatment of mite-allergic asthma. However, guidelines and reviews provide ambiguous recommendations for mite allergen avoidance [4–6], reflecting a lack of consensus in this research field. This lack of consensus on the effectiveness of mite allergen avoidance is summarized by a Cochrane review [7], which was unable to demonstrate any clinical benefit of avoidance measures designed to reduce mite exposure in 55 trials. In addition to the substantial meta-analysis by Gøtzsche and Johansen [7], several other meta-analyses on mite allergen avoidance for the treatment of asthma report varying results for the effectiveness of avoidance [8–11]. The variation in the complex interventions as well as the heterogeneity of several study outcomes urges further exploration [12, 13].

The baseline data are a not well reported in the meta-analyses on the effectiveness of mite allergen control. These baseline characteristics provide attributes for evidence-based decision making in the daily practice of clinicians [14]. First, in the case of asthma, baseline characteristics are of particular interest because they reflect the level of asthma control and the asthma severity of the patient [15]. Studies still highlight the disparities between the asthma severity results between clinical trials and those reported from patient practice [16]. Treatable traits have been defined in severe asthma patients and may be associated with future exacerbation risk [17]. Second, baseline environmental aspects can influence the treatability of allergen-induced asthma [18]. Third, baseline characteristics provide statistical independence in the asthma outcomes of interest. This quantitative factor relates to the possible relationship between exposure and asthma outcomes; for example, in the paradigm of the bedding site introduced in the 1990s [19]. In such cases, the quantitative evaluation of the clinical effectiveness of the treatment of asthma in a meta-analysis differs from that of the traditional two-sample test [20]. These aspects demonstrate that baseline characteristics in a meta-analysis are important for the interpretation of the study results [21].

This study updates and extends the existing Cochrane review by Gøtzsche and Johansen [7], with a focus on baseline asthma outcomes and allergen exposures.

METHODS

Searches and selections

The starting point for this protocol was the Cochrane review by Gøtzsche and Johansen [7]. This meta-analysis includes 55 trials. An updating search was performed in the EMBASE, Medline, and Cochrane databases (see Appendix 1). The titles and/or abstracts of the retrieved updated studies were screened in Endnote by the first author to identify randomized trials that met the inclusion criteria. Searches and selections were checked by a second author (NWJ). We selected all trials by applying the following inclusion criteria; where possible, criteria derived from Gøtzsche and Johansen [7] was applied.

- The study was published in the English language.
- The study was a peer-review publication with full text (no abstracts).
- The study was a randomized controlled trial with blinding.
- The control included a placebo or no treatment (by Gøtzsche and Johansen [7]).
- The participants were physician-diagnosed with bronchial allergic asthma. These included participants who underwent a mite sensitization assessment with either a skin test or serum assay for specific IgE antibodies (by Gøtzsche and Johansen [7]). The asthma assessment included a history of asthma symptoms and a pulmonary function test.
- The intervention was designed to reduce the exposure to mite antigens in the home for the treatment of asthma (mono-trigger therapy by tertiary avoidance). This could include one of the following (by Gøtzsche and Johansen [7]):
  a. Chemical (acaricides);
  b. Physical (mattress covers, vacuum-cleaning, heating, ventilation, freezing, washing, air-filtration, and ionisers);
  c. A combination of chemical and physical.

The flow chart of the updating search was made by use of the PRISMA diagram [22].

Data extraction

The data extraction was elaborated by the first author (FvB); the extracted data included the study population, the type of intervention and control (the strategy of avoidance [13]), the study methodology (randomization and blinding), and outcomes. The outcomes included the
main outcomes and the additional outcomes.

Main outcomes

- Mite allergen load from the mattress (µg/g dust).
- Asthma symptom score diaries (e.g. ASS/ACQ).

- Forced expiratory volume in 1 s percentage of predicted (%) (FEV_1 %pred.)
- Histamine or methacholine concentration that causes a 20% reduction in the FEV_1 (PC_{20}).

Additional outcomes
- Medication usage (use of inhaled corticosteroids: yes or no).
- Type of patient (child or adult).
- Presence of co-sensitization

Missing data were requested from the study authors. A second author (NWJ) validated the selections and the data extraction by the first author. Any ambiguities in the selections and the extractions were resolved by discussion.

The mite allergen load in trials was measured by the allergen content, the number of mites or the guanine content. A rapid colorimetric test such as the Acarex® test can be used to measure the latter. Mite allergen exposure measured by Acarex® or an equivalent test was excluded from the analysis; the Acarex® test is poorly correlated with allergen content [23]. To estimate the allergen load from the number of mites in mattresses, the mean number of mites can be divided by a factor of 50. This ratio is adapted from a nonsensitization threshold for allergens and for mites [24]. However, confidence limits for this calculation are unknown. We therefore also excluded mite counts. The most reliable way to measure the allergen content is with a chemical assay; the Enzyme-Linked Immuno Sorbent Assay (ELISA). In an ELISA the house dust mite allergens in the dust extract binds to an antibody, and are consequently linked to an enzyme, producing a detectable signal correlating to the antigen concentration in the extract [25]. This assay has been the most acceptable assay since 1989 [26]. We limited the studies to those measuring the mass (µg/g dust) of the mite allergen loads in mattresses with ELISA. Early epidemiologic studies defined a threshold level of 10.0 µg mite allergen per gram of dust, above which asthmatic patients are in risk of asthma attacks [24]. Confidence boundaries were absent, reducing the threshold to a rule of thumb. Since then, there is a lack of papers on this threshold level, and thus never updated.

Questionnaires have been developed to measure asthma symptom scores and the adequacy of asthma control, regarding shortness of breath, wheeze, woken by asthma, severity of asthma in the morning, limiting activities because of asthma, use of a short-acting bronchodilator [27]. A limitation of the ASSs is that are no validated cut-off points indicating severity or level of control. In the validated questionnaire by Juniper, an ACQ of 1.50 (maximum 6) relates to inadequately controlled asthma, [28], corresponding to a standardized cut-point of 0.25. The FEV_1 measures the obstruction in the airways during a forced expiratory flower using a spirometer (15). An FEV_1 %pred. of 50 to 79% refers to moderate airflow obstruction, and < 50% to (very) severe obstruction [29].

In a standardized bronchoprovocation test, the dose histamine or methacholine is determined causing a 20% fall in FEV_1, PC_{20} or PD_{20} [30]. A PC_{20} < 1 mg/mL is considered a severe airway hyper responsiveness, and > 8 mg/mL as being a normal responsiveness [31].

The analysis was limited to the main health outcomes with the most reported units. In the case of the ASS, we a priori standardized (SMN) the mean (MN) score by dividing it by the maximum number of the score (MAX). The variance was standardized in the same way (SD^2 standardized = SD^2 extracted/(MAX^2 * number of patients)).

Risk of bias assessment

Gøtzsche and Johansen [7] judged the adequacy of the allocation concealment according to the Cochrane guidelines [32]. Their assessment was not included in the data synthesis. The trials selected for the updated analysis were assessed similarly for the risk of bias by the first author (FvB) using the Cochrane checklist [32]. A second author (NWJ) validated the assessment by the first author. Any ambiguities in the assessed risk of bias were resolved by discussion. We also did not include the assessments in the data synthesis, as we did not hypothesize that the risk of bias or the quality of trials would affect the baseline characteristics.

Statistical and sensitivity analyses

The effect size was set as the mean for the physiological outcomes. The ASSs were standardized. First, the overall effect of the three health outcomes was estimated using a random-effects meta-analysis. Additionally, the I^2 value was calculated to examine heterogeneity in the outcomes. A random-effect meta-regression and subgroups were introduced for all medical outcomes showing at least moderate heterogeneity. Covariates and subgroups of interest included the mite allergen load from the mattress at baseline and possible confounding by the use of inhaled corticosteroids, the type of patient (child/adult), and the presence of co-sensitization. Random-effects meta-regressions and subgroups were tested for a preferred minimum of ten trials (32). Another sensitivity analysis yielded the exclusion of possible outliers as well as the results of the updated reference search. All calculations were performed with the metafor 2.0.0 package in R 3.5.3. [33, 34]. The level of significance was set to $\alpha = 0.05$.

RESULTS

Selection of references

The selection and inclusion of studies resulted in two groups of publications. The first group included the trials from the Gøtzsche and Johansen [7] analysis (fifty-five trials published until July 2011 [35–89]). We excluded twelve of these trials for being only abstracts, being published in a non-English language, not reporting data on the treatment of mite-allergic asthma, or containing non-usable data (outcomes not of prior interest; incomplete data) [35–45, 87]. One of the excluded trials was a large trial by Woodcock et al. [87], which dominated the meta-analysis by Gøtzsche and Johansen (weight > 40%). Woodcock et al. [87] reported incomplete data in the subset of the mite load as well as the ASS. Further, the research team did not report the FEV_1 or the PC_{20} data. The remaining forty-three trials were included for data extraction. The second group included studies identified in our updated search starting in July 2011 (Figure 1). We found a total of 942 titles and abstracts. Nine hundred and fifteen titles were excluded for not reporting a randomized blinded trial on the effectiveness of tertiary mite allergen avoidance. Twenty-eight potentially relevant titles were selected for inclusion [90–117]. Twenty-six full-text articles were excluded for not meeting our inclusion criteria (see Appendix 1). Two full-text articles were included in the analysis [97, 115]. Finally, forty-five full-text articles were included in the analysis.

Description of the included trials

Thirty-nine trials reported avoidance using concurrent bedroom intervention strategies, and six trials reported air purification strategies. In twenty-five trials (56%), patients used inhaled corticosteroids at baseline. Twenty-one trials reported on the treatment of children with allergic asthma, the other twenty-four reported on the treatment of adults; some trials included both children and adults. In nineteen trials, co-sensitization at baseline was reported. Gøtzsche and Johansen [7] previously reported that eight of the included trials had a low risk of bias. Seven trials were judged to have a high risk of bias. The bias in the remaining twenty-eight trials was deemed unclear by Gøtzsche and Johansen [7]. We judged the trial by El-Ghitany and El-Salam [97] to have an unclear risk of bias [no information on concealment was included]. The trial by Murray et al. [115] was judged to have a low risk of bias (use of a computerbased minimization procedure).

Mean characteristics at baseline

Seventeen of the forty-five trials reported on the mite allergen load from the mattress at baseline, as measured by ELISA (mean 9.86 μg/g dust; 95% CI: 5.66 to 14.05 μg/g dust; range 0.44 to 24.83 μg/g dust; n = 1066; I^2 = 99.8%; Figure 2). The standardized ASSs at

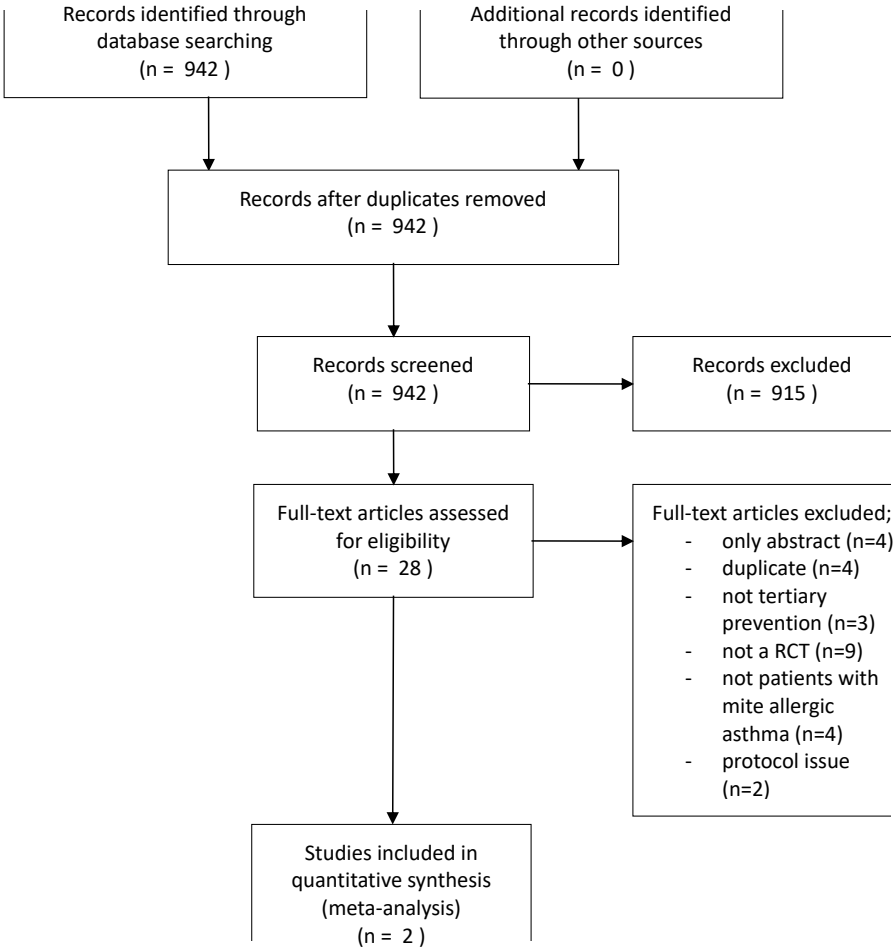

Figure 1. Flow chart of the updating literature search and selection of studies

baseline were reported in twelve trials with high heterogeneity (standardized symptom score = 0.13; 95% CI: 0.08 to 0.18; range: 0.03 to 0.29; n = 703; I^2 = 99.9%; Figure 3). Sixteen studies reported the outcome FEV_1 %pred. by measuring the percentage predicted value (FEV_1 %pred. = 85.3%; 95% CI: 80.5 to 90.1%; range 68.5 to 102.2%; n = 816; I^2 = 95.8%; Figure 4).

Fifteen trials reported PC_{20} values at baseline, expressed as mg/mL. The mean PC_{20} was 1.69 mg/mL (95% CI: 0.86 to 2.52 mg/mL; n = 599; I^2 = 95.6%, Figure 5).

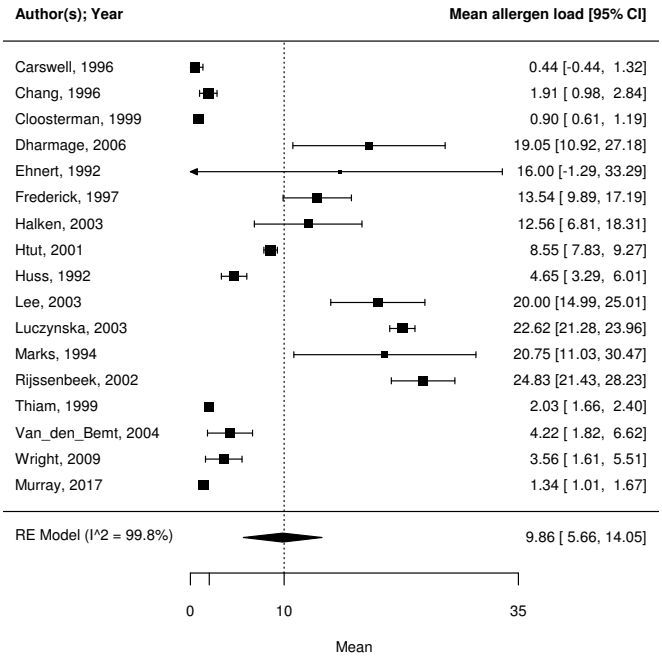

Figure 2. Forest plot of the mite allergen load of the mattress at baseline

Dependence, subgroups and sensitivity analysis

The covariate mite allergen load at baseline did not significantly influence the health outcomes (standardized ASSs: P = 0.13; FEV_1 %pred.: P = 0.81; PC_{20}: P = 0.75, see Appendix 1). We calculated the FEV_1 %pred. in the adult subgroup (FEV_1 %pred.; adults = 84.2%, 95% CI: 79.2 to 89.2%; 11 trials). All other subgroups included less than ten trials. Finally, the random-effects models for the health outcomes were unaltered when excluding the updated trials (symptom score 0.12; FEV_1 %pred.: 85.4%; PC_{20}: 1.69 mg/mL).

DISCUSSION

This study contributes to the existing Cochrane review by Gøtzsche and Johansen [7] by generating hypotheses on the characteristics of asthma outcomes according to baseline data as well as possible dependencies for asthma outcomes. We observed considerable heterogeneity in the mite allergen load in the mattresses (17 trials), the standardized ASSs (12 trials), the FEV_1 %pred. values (16 trials), and the PC_{20} values (15 trials). We judged the mean mite allergen load from the mattress at baseline to be moderate (9.86

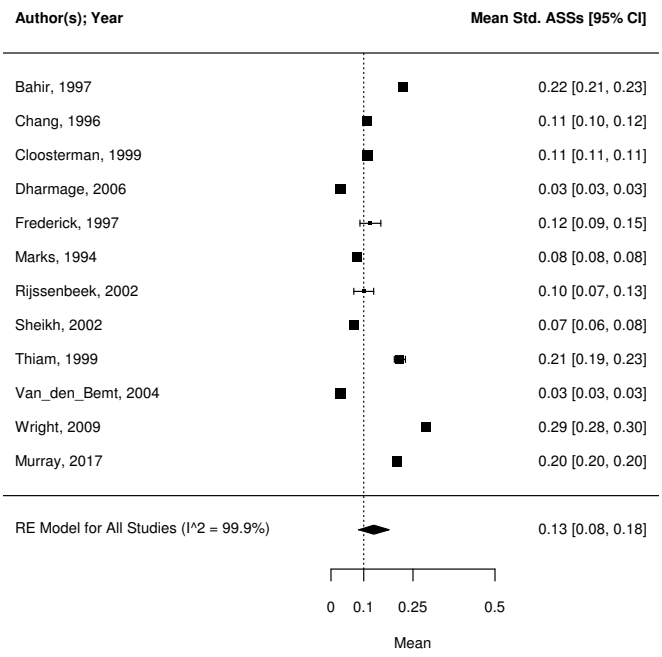

Figure 3. Forest plot of the standardized asthma symptom scores at baseline

μg/g dust). Overall, the standardized ASSs and the percentage predicted FEV_1 %pred. suggested a mild to moderate disease. The PC_{20} at baseline predominantly indicated moderate to severe airway hyperresponsiveness according to the definition by Cockroft [31]. We did not observe a relationship between the mite allergen load from the mattress at baseline and health outcomes. The number of trials available did not allow for comparisons between the child and adult subgroups, the inhaled corticosteroid use or no use subgroups, or the presence or absence of co-sensitization subgroups.

In this study, we observed several factors related to the three attributes of prior interest. The first attribute was asthma severity. We observed a mild to moderate magnitude of asthma severity at baseline. We were, however, limited in our evaluation of asthma severity by the absence of appropriate instruments to assess asthma control [27, 118] and the asthma-related quality of life [119]. Compatible with the situation of pharmacological treatments [16], it remains unknown whether the results found by Gøtzsche and Johansen [7] are generalizable to patients with uncontrolled asthma. In one trial [55], we extracted a median symptom score at daytime of zero for the treatment group. Since the score was already zero at baseline, it was probably clear that there would be no clinical benefit observed in this subset. The asthma outcomes showed more notable levels, such as a FEV_1 %pred. above 100%, as reported by Carswell et al. [51]. The moderate asthma status

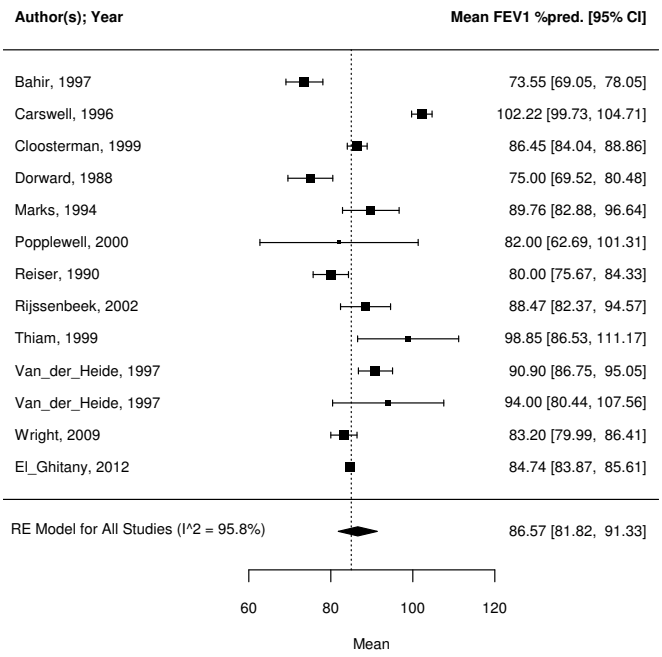

Figure 4. Forest plot of the FEV_1 percentage of predicted at baseline

at baseline was possibly related to the use of inhaled corticosteroids, as reported in more than half of the included trials [56%]. However, the number of trials available did not allow for testing this hypothesis.

A second attribute is the magnitude of the exposure at baseline, which relates to the environmental treatability. In four of the included trials [51–53, 115], we observed that the mean mite allergen load from the mattress at baseline was quite low [range 0.44 to 1.91 μg/g dust]. Only one of these four trials included an evaluation of the treatability of mite allergen exposure at baseline in their methods [52]. Environmentally, whether such low values of exposure are considered treatable remains a question. An exposure level of 0.44 μg/g dust is quite similar to the exposure level observed in the "low-allergen" region of Davos in the European Alps (approximately 0.02 to 0.2 μg/g dust; assessed from [120]). In addition, Pingitore and Pinter [121] noted that in many trials, there was no success in reducing the mite allergen load. Overall, it seems that multiple clinical trials on avoidance paid little attention to the environmental issue of the treatability of the exposure.

Furthermore, the attribute of dependence was of interest in this study. None of the medical baseline data could be related to mite allergen exposure from the mattress. This indicates that from a meta-viewpoint, at baseline, there was no clinical potential for reducing the mite allergen load in the bedding.

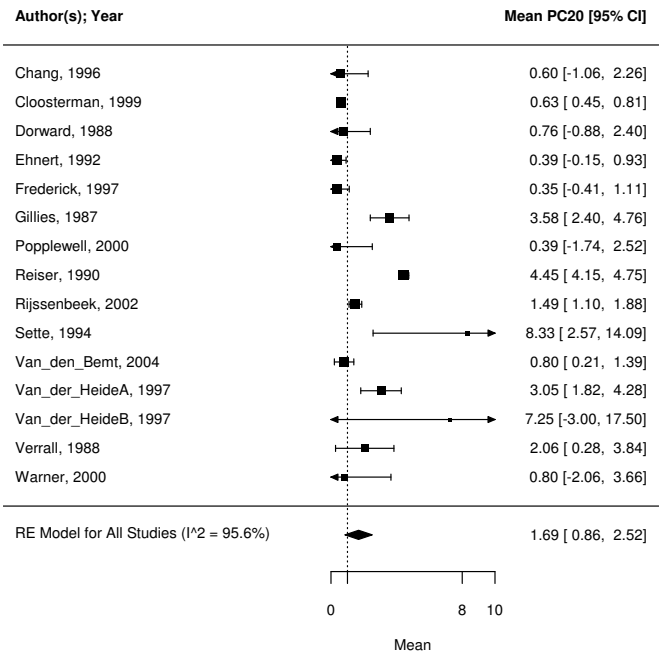

Figure 5. Forest plot of the PC_{20} at baseline

As far as we know, this is the first systematic review of baseline characteristics in trials on mite allergen avoidance for the treatment of asthma. This study was executed a priori to generate hypotheses for a new meta-analysis on the treatment of mite-allergic asthma by environmental control. Generating hypotheses to define a protocol for a meta-analysis prevents misleading conclusions [32]. We could not generate a hypothesis on a possible relationship with asthma outcomes, particularly considering the mite allergen exposure covariate. The mite allergen load from the mattress covariate was limited to the data obtained from ELISA. This limitation can be considered a rigorous selection factor to prevent bias in this covariate of prior interest. It is possible that some of the covariates we used were still unrefined. For instance, the covariate co-sensitization was introduced as a binary value (presence yes or no); we believe the next step is to introduce the number of co-sensitizations as an ordinal covariate.

The main limitation of this study was that we had to exclude the large trial by Woodcock et al. [87] because their data was not usable data for the purpose of this study. Woodcock et al. did probably not include patients with uncontrolled asthma. Their publication included only adult patients with asthma who were undergoing routine management with inhaled corticosteroids in primary care. Though not a limitation, another large trial also worth noting is the recently published study by Murray et al. [115].

Murray et al. found that only the use of single covers prevented asthma exacerbations in the hospital setting. In a post hoc analysis, Murray et al. reported that relatively younger children (P = 0.006), those mono-sensitized to mites (P = 0.04), those with severe asthma (P = 0.03), and those not exposed to smoking (P = 0.02) explained the reduced number of hospital admissions in the 123 participants. No information was presented on the selection of significant covariates or on the power of the calculations. Possibly, the results by Murray et al. [115] are explained by a more severe asthma status at baseline than those in the participants in the trials included by Gøtzsche and Johansen [7].

The baseline characteristics in a meta-analysis have been the subject of methodological studies, emphasizing the careful consideration of this topic in the definition of the protocol [21, 122]. Advanced statistical methods to evaluate underlying risk have been developed for cases in which the baseline characteristics or the severity of the disease among the participants varies [123]. The definition of the types of participants is considered a key factor in reviews [32]. A positive example of the explicit (a priori) consideration of baseline characteristics was demonstrated in the Cochrane review on the treatment of asthma by sublingual immunotherapy [124]. In contrast, the current meta-analyses on the treatment of asthma using avoidance were commonly characterized by no baseline characteristic reporting [7–11]. Gøtzsche and Johansen [7] stated that adjusting for baseline differences would risk biasing the review, "since investigators are inclined to show baseline differences and adjust for them when this procedure favours the experimental treatment". By limiting their meta-analysis to the changes and final values, Gøtzsche and Johansen [7] did not account for the types of participants they reviewed. Other Cochrane reviews on the treatment of asthma or rhinitis by mite allergen avoidance [125, 126], recognized for their rigorous methodology, do not account for the types of participants, as they did not describe their baseline characteristics. This suggests that there is room for improvement in the multiple Cochrane reviews and other meta-analyses on avoidance.

In conclusion, this systematic review demonstrates that many previous mite avoidance studies are characterized by the inclusion of patients with rather mild to moderate asthma and with varying and sometimes negligible levels of allergen exposure. Most likely, the use of asthma medication modified the baseline asthma outcomes in these studies, leaving less room to improve. In future studies, we suggest focusing on patients with partially controlled or uncontrolled asthma and assessing asthma control with the appropriate instruments [27, 118, 119]. Moreover, to test the efficacy of allergen avoidance, sufficient mite exposure at baseline should be present. In the absence of an evidence-based threshold level, we suggest the provisional use of the formerly defined rule of thumb that suggests that 10.0 μg mite allergen per gram of dust is relevant to asthma symptoms [19].

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CHAPTER 3

The strategies of house dust mite allergen avoidance

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A reintroduction of environmental mite allergen control strategies for asthma treatment and the debate on their effectiveness.
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ABSTRACT

Asthma affects three hundred million people worldwide. The effectiveness of house dust mite allergen control for asthma treatment is debatable. One aspect that has been little discussed in existing meta-analyses is the possible role of environmental strategies. Here, we reintroduce the previously defined strategies for mite allergen control and discuss their importance to the debate on clinical effectiveness. The strategy of concurrent bedroom interventions is related to the combined use of a priori defined interventions, while the strategy of exposure-based control relates to the treatment of relevant textiles after assessing exposure. The air purification strategy aims to purify the human breathing zone of airborne allergens. In Western European patient practice, the use of these strategies differs. A post hoc study of the dominant Cochrane review by Gøtzsche and Johansen (Cochrane Database of Systematic Reviews, 2008, Art. No: CD001187) appears to indicate that a majority of the underlying trials reported on the strategy of concurrent bedroom interventions, which were mainly executed in a minimal manner. Some trials have reported on the air purification strategy and may potentially alter the debate on effectiveness. No trial has reported on the strategy of exposure-based control. We therefore hypothesize that the absence of evidence for the effectiveness of mite allergen control for asthma treatment applies to the strategy of concurrent bedroom interventions. The evidence-based effectiveness of the exposure-based control strategy appears to be undetermined. The results of our post hoc reanalysis urge that future meta-analyses of mite allergen control should a priori define the environmental strategy under study. Future trials of mite allergen control are warranted to test the exposure-based strategy as well as the sparsely tested strategy of air purification.

INTRODUCTION

Asthma affects hundreds of millions of people worldwide, and its prevalence is still rising [1,2]. The role of house dust mite allergy in asthma is evident; however, it is not exclusive [3]. Therapies have been developed for the treatment of allergic asthma, including avoidance of mite allergen exposure, immunotherapy and pharmacological treatment [4]. However, the effectiveness of mite allergen control has become debatable [5], and existing guidelines show a lack of consensus on mite allergen control [6-8]. Therefore, gaining knowledge of the clinical effectiveness of avoiding allergen exposure should still be considered a research priority compared to controlling other types of exposure [9,10].

The debate on the effectiveness of mite allergen control for the treatment of asthma has not been characterized by progress. For instance, repeated comments have been made on the meta-analysis by Gøtzsche et al. [5,11,12], pointing to the benefits of multiple trigger therapy in a large trial [13]. However, these types of comments have previously been rejected by Gøtzsche et al. [14], who said: "none of the correspondents have provided data (at the same level of evidence) to the contrary". Nevertheless, investigators [15] continue to mention the benefits of trials excluded previously by Gøtzsche and Johansen [16]. One novelty seems to be the introduction of a hypothesis by Tovey and Ferro that the debate on effectiveness calls for personalized avoidance by a better understanding of the nature of allergen exposure [17].

A little-discussed aspect of the question of clinical effectiveness is the role of mite allergen control strategies. Strategies have been defined to avoid house dust mite allergen exposure (see the section "Strategies for mite allergen control"), including total avoidance [18], exposure-based control [19], concurrent bedroom interventions [20], purification of the breathing air [21], and a sojourn in a mite-free [alpine] environment [22]. Environmentally, the reduction in exposure by different strategies is not necessarily equivalent. It remains unclear whether the absence of evidence of the clinical effectiveness of mite allergen control relates to any particular strategy. In this review, we reintroduce previously defined strategies for mite allergen control and discuss their importance to the debate on clinical effectiveness, including future investigations.

STRATEGIES FOR MITE ALLERGEN CONTROL

Initial strategies

Among mono- and multi-trigger approaches [23], strategies can be considered to control exposure to house dust mites and their allergens. Prior strategies have related to the removal of the patient to a mite-free environment. A sojourn in a Swiss alpine mite-free environment has been used more than a hundred years and shown to benefit asthmatic

patients temporarily [22]. Platts-Mills et al. [24] removed patients for 2 months or more to a dust-free hospital environment, resulting in significantly reduced bronchial hyperreactivity. These prior strategies were continued by the strategy of total avoidance of the home environment of the asthmatic patients. This strategy of total avoidance has defined a combination of measures aiming for an indoor environment completely free of living and dead house dust mites as well as their faecal products [18,25]. The measures developed have included mainly acaricidal products and mite-impermeable covers. However, it became clear that the strategy of total avoidance is rarely achievable by patients in the long term [26].

Textile-based strategies

Meanwhile, strategies were defined to gain the benefits of rigorous and intensive total avoidance using a more efficient approach. Colloff [20] defined a set of a priori defined barriers, called integrated avoidance. We redefine this approach as the strategy of concurrent bedroom interventions: a combined approach aimed at controlling house dust mite exposure by primarily treating the bedroom environment with a priori defined barriers. The original strategy comprises a total of seven barriers. In a more recent publication, Colloff updated the strategy to nine barriers [27]. The five primary barriers consist of (a) fitting of mite-impermeable covers to all bedding; (b) monthly hot laundering of the bedding; (c) removal of the bedroom carpet; (d) weekly vacuuming of other textiles with a high-efficiency particulate air (HEPA) filter vacuum cleaner; (e) removal of upholstered furniture, rugs, mattresses, and bedding to the outside environment for 12 hours to dry, heat and/or freeze, followed by vacuuming. An alternative is presented if a primary barrier cannot be executed (four alternatives). The strategy of concurrent bedroom interventions as positioned by Colloff [20] garnered less attention (three citations, Google Scholar, retrieved October 21, 2018). This strategy was introduced at the conference Mites, Asthma and Domestic Design II in Sydney.

Around the same period, van Bronswijk [19] introduced the strategy of selective avoidance. We redefine this strategy as exposure-based control: a combined approach based on the assessment of the actual exposure in the home environment, followed by the extermination of mites and removal of all relevant sources of allergenic dust. This strategy assumes the existence of a hygienic threshold for allergen exposure above which symptoms will develop (2 μg/g dust) [25]. A simplecolorimetric test was introduced in patient practice that related the actual exposure in the home environment to the hygienic threshold [28]. In the worst case, the exposure-based strategy results in total avoidance of the home environment. The strategy of exposure-based control gathered only two citations (Google Scholar, retrieved October 22, 2018). We hypothesize that the low number of citations is due to the publication of this strategy at a conference (International Conference on Insect Pest in the Urban Environment, Cambridge) rather than a peer-reviewed journal.

The measures that constitute the textile-based strategies can be differentiated into short-term and long-term measures. Short-term measures aim to directly reduce allergen exposure, such as the use of chemical products or washing textiles at 60 °C [18]. These types of measures must be repeated throughout the year. Long-term measures aim to control allergen exposure only after one or more climatic seasons by lowering the relative humidity in niches during the heating season (cold climates) or by airing textiles outside during the summer (hot climates) [27-29]. Humidity control is an environmental intervention aiming to eradicate living mites but not directly the allergenic mite faeces [19]. The mite faeces remain allergenic for a very long time [30], thus urging humidity control for use in conjunction with co-acting environmental methods [27]. We judge the sole intervention of humidity control as a general improvement of indoor air quality (fresh air) by reducing indoor humidity levels [31] but not aiming at the primary control of mite allergen exposure. In addition to improving the general quality of the indoor air, long-term measures are useful for reducing the need to repeat short-term measures with high frequency. The reduced need for repeated intensive cleaning of the home makes mite allergen control more achievable by patients in the long term.

Breathing-zone-related strategies

While both the concurrent bedroom interventions strategy and the exposure-based strategy focus on the elimination of allergen emissions from textiles, the air purification strategy aims to purify the human breathing zone of airborne allergens by use of a HEPA filter capturing at least 85% of particles with a diameter of 0.3 μm [32]. Particles of larger size, such as mite faeces (diameter approximately 10 to 40 μm [33]), are captured at a higher percentage. HEPA filters can be used at varying environmental settings, from a laminar airflow in the breathing zone during sleep [34] to the use of portable devices in the bedroom [35] or an air filtration unit in the living room [36].

Mixed strategies

Finally, we introduce mixed strategies, referring to a combination of strategies that differ in aim or therapy, such as combining the effectiveness of steroids, immunotherapy, and impermeable covers from different trials in one meta-analysis without subgrouping. We consider the mixed strategies somewhat unwieldy. Even if they are clinically effective, the results of mixed strategies are less usable or less efficient for patient practice, particularly when a strategy is not completely executed. For instance, patient practice does not combine a partial impermeable cover with a partial HEPA filter. An exception is the case when all data from a study result from concurrent and completely executed strategies. Therefore, insight into the effectiveness of a single strategy is relevant for evidence-based clinical decision making.

EVIDENCE SUPPORTING THE STRATEGIES

List of meta-analyses

In the section above, we reintroduced the environmental strategies for mite allergen control. After the introduction of textile-based strategies in the early 1990s, the first meta-analysis was performed to assess the effectiveness of mite allergen control at the highest level of evidence [5]. This meta-analysis was later continued in a Cochrane review [37]. In this meta-analysis, Gøtzsche and Johansen included trials on mite-impermeable covers as well as air purification; thus, they investigated a mixture of strategies. The next meta-analysis studied the effectiveness of purifying the air using air filtration for the treatment of allergic asthma [38]. All treatment groups investigated included the use of a HEPA filter, sometimes combined with mite-impermeable covers. The HEPA filters were studied in varying environmental settings. Macdonald et al [39] studied the effectiveness of textile-based strategies for the primary and tertiary prevention of asthma. They reported on the number of days ill due to asthma and a lung function parameter combining the FEV_1 with the peak flow [39]. Campbell and Gibson attempted to study the effects of feather bedding, but the selected trials did not meet the inclusion criteria [40]. In another Cochrane review, Singh and Jaiswal [41] studied the effectiveness of humidity control for the treatment of asthma. We believe that the environmental strategy studied by Singh yields a general improvement of indoor air quality (fresh air) but not mite control. Crocker et al. [23] investigated the effectiveness of home-based multi-trigger interventions. The meta-analysis by Crocker et al. [23] included a small number of patients with house dust mite allergic asthma (34%). Three meta-analyses on the effectiveness of concurrent bedroom interventions using mite-impermeable covers were introduced in 2014. Arroyave et al. [42] included seven trials on the treatment of asthma. In the same year, van Boven [43] generated a hypothesis regarding the effectiveness of mite-impermeable covers using a meta-analysis. Van Boven [43] limited the intervention to trials that covered all bedding elements (mattress, duvet, and pillow), fitting it to the definition of the strategy of concurrent bedroom interventions [27]. Huiyan et al. [44] investigated six trials on mite-impermeable covers combined with one trial on humidity control. Three of the trials investigated by Huiyan et al. [38-44] were also included in the analysis by Gøtzsche and Johansen [37]. To some extent, many meta-analyses can be considered to represent subsets of the large meta-analysis by Gøtzsche and Johansen [37].

Clinical effectiveness

Clinical benefits in patients with house dust mite allergy-related asthma were reported by small meta-analyses. McDonald et al. [38] reported a significant standardized mean difference in the asthma symptom score (95% CI: -0.69 to -0.25; 88 patients) and the sleep disturbance (95% CI: -1.44 to -0.42; 47 patients). Macdonald et al. [39] found a

positive reduction in the number of days ill (95% CI: –0.59 to –0.13 by two trials). Van Boven [43] observed that the more bedroom interventions were combined, the higher the reduction in the mite load from the mattress when the load was high at baseline (P = 0.02; nine trials). Among the listed meta-analyses, the meta-analysis by Gøtzsche and Johansen [37] dominates the debate. While Gøtzsche and Johansen were unable to demonstrate any clinical benefit based on 55 trials, Bousquet et al. [45] concluded from this meta-analysis that the use of a single intervention measure is not effective. Pingitore and Pinter [46] mentioned that Gøtzsche and Johansen included trials reporting no reduction in mite allergen exposure. As the meta-analysis by Gøtzsche and Johansen [37] reports on a mix of strategies without subgrouping, the role of the specific strategies remains unclear.

THE POSSIBLE ROLES OF STRATEGIES IN EFFECTIVENESS: AN EXAMPLE

Methods

The debate on effectiveness is dominated by the large and rigorous meta-analysis by Gøtzsche and Johansen [37]. This meta-analysis on a mix of strategies did not subgroup for possible differences between mite allergen control strategies. We post hoc subgrouped the results by Gøtzsche and Johansen [37] into categories based on the environmental strategy used for mite allergen control. The extractions as published by Gøtzsche and Johansen [37] were the basis of this reanalysis. Outcomes were limited to the number of patients improved, the medication usage, the asthma symptom score, the forced expiratory volume in one second (FEV_1), and the histamine or methacholine concentration that caused a 20% reduction in FEV_1 (PC_{20}). The assessment of the type of strategy as studied in the underlying trials yielded three judgements:

- Assessing the strategy used to control mite allergen exposure. The strategy was defined as "concurrent bedroom interventions" for any a priori defined intervention aimed at reducing the mite allergen load while not assessing the relevant sites of exposure in the home environment.
- If the intervention was judged to follow the strategy of concurrent bedroom interventions, we assessed the number of barriers used.
- If the strategy of concurrent bedroom interventions was not followed consequently, the number of barriers was set at one. For instance, the single treatment of a carpet in the living room was judged as one barrier (Barrier 4: Vacuuming of other textiles).

Effect sizes were calculated by a random-effects model with the metafor package 2.0.0 [47] in R (version 3.4.1) [48]. Subgroup analysis yielded a calculation of the effect size related to the environmental control strategy. We continued subgrouping the strategy of concurrent bedroom interventions to the use of one barrier or two or more barriers. For other statistical aspects, we referred to the original study by Gøtzsche and Johansen [37]. The level of significance was set to $\alpha = 0.05$. The magnitude of the standardized mean difference (SMD) was judged to be small for an SMD of 0.2, medium for an SMD of 0.5, and large for an SMD of 0.8 [49].

Results of the subgrouping analysis

Gøtzsche and Johansen [37] investigated mixed strategies in 55 randomized trials (concurrent bedroom interventions, air purification, and combinations). Thirty-six of these trials reported on one or more outcomes of interest (Table 1; Ref. 34-36; 50-82). Thirty trials tested an intervention based on the strategy of concurrent bedroom interventions, of which twenty-three interventions were classified as one barrier (77%). Seven trials were classified as investigating two or three barriers (23%). Six trials investigated the air purification strategy. No trial reported on an investigation of the strategy of exposure-based control. The remaining subgroups that reported on one barrier (concurrent bedroom interventions) included a total of 3031 patients (74%), the subgroups that reported on two or more barriers included 817 patients (20%), and the subgroups that reported on air purification included 258 patients (6%).

The SMD in asthma symptom scores ranged from SMD = -0.03 to -0.53, with all P-values ranging from 0.19 to 0.87 (Table 2). Heterogeneity ranged from $I^2 = 54\%$ to 91%. For FEV_1, the SMD ranged from +0.07 to +0.17, with P-values ranging from 0.08 to 0.81 and negligible heterogeneity ($I^2 = 0$ to 28%) (Table 3). Three subgroups reported on PC_{20} outcome, with the SMD ranging from -0.12 to +0.05 (P =0.45 to 0.80) (Table 4). The subgroups showed no heterogeneity ($I^2 = 0\%$). For medication usage, two subgroups reported an SMD = -0.04 to -0.17 (P = 0.46 to 0.49; $I^2 = 0\%$) (Table 5). The risk ratio for the number improved in the subgroups of concurrent bedroom interventions was 0.85 to 1.07 (P = 0.77 to 0.87), with an absence of heterogeneity (Table 6). In the subgroup of air purification, we found a non-significant risk ratio of 0.67 (P = 0.61), with an absence of heterogeneity.

Table 1. Environmental strategy categories of the trials studied by Gøtzsche and Johansen [37]

Trial	Author	Year	Strategy	Barriers	Remark
1	Antoniceli	1991	Air purification	NA	
2	Bahir	1997	Concurrent bedroom	1	
3	Burr	1980A	Concurrent bedroom	1	
4	Burr	1980B	Concurrent bedroom	1	
5	Carswell	1996	Concurrent bedroom	3	
6	Chang	1996	Concurrent bedroom	1	
7	Chen	1996	Concurrent bedroom	1	
8	Cinti	1996	Concurrent bedroom	1	Strategy extracted from description by Gøtzsche and Johansen
9	Cloosterman	1999	Concurrent bedroom	2	
10	De_Vries	2007	Concurrent bedroom	1	
11	Dharmage	2006	Concurrent bedroom	1	
12	Dieteman	1993	Concurrent bedroom	1	
13	Dorward	1988	Concurrent bedroom	1	
14	Ehnert	1992	Concurrent bedroom	2	
15	Fang	2001	Concurrent bedroom	1	
16	Geller-Bernst	1995	Concurrent bedroom	1	
17	Halken	2003	Concurrent bedroom	1	
18	Htut	2001	Concurrent bedroom	1	
19	Huss	1992	Concurrent bedroom	1	
20	Kroidl	1998	Concurrent bedroom	1	
21	Maesen	1977	Air purification	NA	
22	Marks	1994	Concurrent bedroom	2	
23	Reiser	1990	Concurrent bedroom	1	
24	Rijssenbeek	2002	Concurrent bedroom	3	
25	Sette	1994	Concurrent bedroom	1	
26	Shapiro	1999	Concurrent bedroom	2	
27	Sheikh	2002	Concurrent bedroom	1	
28	Thiam	1999	Concurrent bedroom	2	
29	Van_der_Heide	1997A	Concurrent bedroom	1	
30	Verrall	1988	Air purification	NA	
31	Walshaw	1986	Concurrent bedroom	1	
32	Warburton	1994	Air purification	NA	
33	Warner	1993	Air purification	NA	
34	Woodcock	2003	Concurrent bedroom	1	
35	Wright	2009	Concurrent bedroom	1	
36	Zwemer	1973	Air purification	NA	

Table 2. Standardized mean differences in asthma symptom scores related to environmental strategy in the meta-analysis by Gøtzsche and Johansen [37]

Strategy	SMD	95% CI	Patients (n)	P-value	I^2
Sojourn high altitude	NA	NA	NA	NA	NA
Total avoidance	NA	NA	NA	NA	NA
Exposure-based	NA	NA	NA	NA	NA
Concurrent bedroom	-0.07	-0.35 to 0.21	1415	0.62	68%
1 barrier	-0.03	-0.37 to 0.32	1169	0.87	54%
2-3 barriers	-0.25	-0.89 to 0.40	246	0.43	91%
Air purification	-0.53	-1.35 to 0.30	70	0.19	68%
Mixed strategies	-0.13	-0.40 to 0.15	1485	0.35	72%
Gøtzsche & Johansen [a]	-0.06	-0.16 to 0.05	1485	0.29	68%

a Standardized mean differences as calculated by Gøtzsche and Johansen [37] with a fixed-effect model.

Table 3. Standardized mean differences in FEV_1 related to environmental strategy in the meta-analysis by Gøtzsche and Johansen [37]

Strategy	SMD	95% CI	Patients (n)	P-value	I^2
Sojourn high altitude	NA	NA	NA	NA	NA
Total avoidance	NA	NA	NA	NA	NA
Exposure-based	NA	NA	NA	NA	NA
Concurrent bedroom	-0.07	-0.35 to 0.21	1415	0.62	68%
1 barrier	-0.03	-0.37 to 0.32	1169	0.87	54%
2-3 barriers	-0.25	-0.89 to 0.40	246	0.43	91%
Air purification	-0.53	-1.35 to 0.30	70	0.19	68%
Mixed strategies	-0.13	-0.40 to 0.15	1485	0.35	72%
Gøtzsche & Johansen [a]	-0.06	-0.16 to 0.05	1485	0.29	68%

a Standardized mean differences as calculated by Gøtzsche and Johansen [37] with a fixed-effect model.

Table 4. Standardized mean differences in PC_{20} related to environmental strategy in the meta-analysis by Gøtzsche and Johansen [37]

Strategy	SMD	95% CI	Patients (n)	P-value	I^2
Sojourn high altitude	NA	NA	NA	NA	NA
Total avoidance	NA	NA	NA	NA	NA
Exposure-based	NA	NA	NA	NA	NA
Concurrent bedroom	0.05	-0.09 to 0.20	475	0.45	0%
1 barrier	0.05	-0.20 to 0.30	254	0.68	0%
2-3 barriers	0.05	-0.21 to 0.32	221	0.69	0%
Air purification	-0.12	-1.05 to 0.80	18	0.80	0%
Mixed strategies	0.05	-0.13 to 0.22	493	0.61	0%
Gøtzsche & Johansen [a]	0.05	-0.13 to 0.22	493	0.61	0%

a Standardized mean differences as calculated by Gøtzsche and Johansen [37] with a fixed-effect model.

Table 5. Standardized mean differences in medication usage related to environmental strategy in the meta-analysis by Gøtzsche and Johansen [37]

Strategy	SMD	95% CI	Patients (n)	P-value	I^2
Sojourn high altitude	NA	NA	NA	NA	NA
Total avoidance	NA	NA	NA	NA	NA
Exposure-based	NA	NA	NA	NA	NA
Concurrent bedroom	-0.04	-0.16 to 0.08	1043	0.49	0%
1 barrier	-0.04	-0.16 to 0.08	1043	0.49	0%
2-3 barriers	NA	NA	NA	NA	NA
Air purification	-0.17	-0.64 to 0.29	72	0.46	0%
Mixed strategies	-0.05	-0.17 to 0.07	1115	0.39	0%
Gøtzsche & Johansen [a]	-0.05	-0.17 to 0.07	1115	0.39	0%

a Standardized mean differences as calculated by Gøtzsche and Johansen [37] with a fixed-effect model.

Table 6. Risk ratios for the number of patients improved related to environmental strategy in the meta-analysis by Gøtzsche and Johansen [37]

Strategy	RR	95% CI	Patients (n)	P-value	I^2
Sojourn high altitude	NA	NA	NA	NA	NA
Total avoidance	NA	NA	NA	NA	NA
Exposure-based	NA	NA	NA	NA	NA
Concurrent bedroom	1.06	0.75 to 1.50	282	0.82	0%
1 barrier	1.07	0.75 to 1.53	233	0.77	0%
2-3 barriers	0.85	0.19 to 3.79	49	0.87	0%
Air purification	0.67	0.24 to 1.87	56	0.61	0%
Mixed strategies	1.01	0.73 to 1.40	338	0.96	0%
Gøtzsche & Johansen [a]	1.01	0.80 to 1.27	338	0.94	0%

a Risk ratios as calculated by Gøtzsche and Johansen [37] with a fixed-effect model.

Discussion of the subgrouping analysis

Overall, post hoc subgrouping shows that the environmental intervention studied in the meta-analysis by Gøtzsche and Johansen [37] relates predominantly to the concurrent bedroom interventions strategy and little to the air purification strategy. A majority of the underlying trials reported on the strategy of concurrent bedroom interventions with one barrier or when performed in an inconsistent manner that was also classified as one barrier. When grouping the outcomes of the strategy of concurrent bedroom interventions as one barrier or two or more barriers, as well as the strategy of air purification, all effect sizes were not significant. The outcome of the asthma symptom score showed a non-significant increase in the SMD, from zero in the subgroup with one barrier to a small effect in the subgroup with two barriers, to a larger effect in the group with air purification.

The opposite of this non-significant increase in the magnitude of the effect size was a decrease in the number of patients, which was low in the subgroup with two barriers (n = 246) and very low in the subgroup with air purification (n = 70). A similar and smaller tendency was observed in the outcome of medication usage. The subgroup with one barrier showed zero effect, compared to a small effect in the subgroup with air purification. However, the number of patients decreased from 1043 in the subgroup with one barrier to 72 in the subgroup with air purification. The absence of significance in air purification may be explained by the small number of patients studied. However, we cannot exclude the possibility that the variation in outcomes played a role. These results suggest that the reintroduction of strategies has the potential to alter the debate on effectiveness. As our analysis was post hoc, it indicates a need to include the strategy of mite allergen control as a factor when defining meta-analysis protocols [83].

GENERAL DISCUSSION

A reintroduction of strategies

This review reintroduces previously defined strategies for mite allergen control. Both the concurrent bedroom interventions strategy and the exposure-based strategy were introduced in the early 1990s. These strategies did not attract much attention by researchers, possibly because these strategies were not published in peer-reviewed journals. Both textile-based strategies built on the first-line reduction or prevention of allergen emissions from textiles are of primary importance in patient practice. Other defined strategies include air purification and a sojourn to an (alpine) mite-free environment. The latter two strategies are sparsely studied and not commonly advised in patient practice, possibly due to their costs. Only the strategy of removing patients from an environment with high mite allergen exposure is clearly accepted as effective [14,24]. Most of the recent meta-analyses of textile-based mite allergen control for the treatment of asthma do not relate their findings to a strategy [37,39,40,42,44].

On textile-based strategies

A post hoc reanalysis of the dominant meta-analysis by Gøtzsche and Johansen [37] suggests that a majority of the trials examined had reported on the use of concurrent bedroom interventions executed in a minimal manner. The exposure-based strategy was not tested in the included trials. This result suggests that it is unknown whether the conclusion by Gøtzsche and Johansen [37] is valid for the exposure-based strategy. In our opinion, the choice of the strategy of concurrent bedroom interventions reflects the principals of traditional clinical trial design [84]. In a clinical experiment, the aim is to test for a possible difference between treatment and no treatment. A secondary aim in a

clinical experiment is to minimize the variance in outcomes to discriminate a treatment effect in as unbiased a manner as possible [85]. Among the many issues playing a role in minimizing variance in a trial, we consider the choice of a predefined simple and homogeneous treatment to be one, for instance, such as the choice of single bedding covers. However, the opposite of minimizing the variance is the considerable heterogeneity present in personal exposure. Studies on personal airborne exposure [86-88] show that relevant average exposure is not necessarily related to the sleeping site. Environmentally, emission sources, emission magnitudes, emission frequencies, and the presence of patients at emission sites may all vary. The considerable variance in exposure in patient practice calls for an exposure-based strategy. Nonetheless, we do not know of any study comparing the (clinical) effectiveness of the frequently tested strategy of concurrent bedroom interventions with the exposure-based strategy. This research question is relevant, as highly skilled health practitioners from France and The Netherlands advise their patients by use of the exposure-based strategy [89,90].

Recent studies

Additionally, recent studies have not related their findings to a specific strategy. Leas et al. [91] systematically reviewed the effectiveness of allergen control by subgrouping the control methods but not the strategies. In the review by Leas et al. [91], the assessment of the effect size remained unclear. Le Cann et al. [92] reviewed the effectiveness of home interventions for the treatment of allergy and respiratory diseases. They subgrouped interventions into three categories: education-based methods, physical methods, and a combination of both. Le Cann et al. [92] reported mixed results of these home interventions, urging further study of a multifaceted approach. Murray et al. [93] investigated the effect of mite-impermeable covers in a large randomized trial (n = 284) for the treatment of severe asthma exacerbations in children. In this trial, Murray et al. [93] reported a significant decrease in the primary outcome of hospitalization, which is sparsely studied in this field. We classified their intervention as the strategy of concurrent bedroom interventions using two barriers. From the observations by Murray et al., we assessed the SMD in asthma symptom score as -0.15 (95% CI: -0.41 to +0.12; P = 0.28), which fitted satisfyingly to our recalculation for the subgroup with two to three barriers.

Developing the debate?

What does our reintroduction of strategies add to the debate on allergen control? As stated above, the debate on the effectiveness of mite allergen control for asthma treatment has not been characterized by progress. Our reintroduction of environmental strategies of mite allergen control continues the call for re-thinking avoidance [17]. This call introduces the idea of improved measurement of personal exposure [88,94], reflecting the strategy of exposure-based control. Exposure-based control was not the subject of

study in any of the trials we analysed post hoc. The post hoc results of the subgroup of air purification are also of interest and have potential to influence the debate. For the concurrent bedroom interventions strategy, a question arises of the effectiveness of an intervention based on the full elaboration of this strategy, as this method has not yet been studied.

Other domains

Investigations on other allergic disorders caused by mites seem to show an identical tendency in strategies. Sheikh et al. [95] conducted a Cochrane review on the treatment of rhinitis and concluded that "extensive bedroom-based environmental control programmes may be of some benefit" and "evidence that isolated use of house dust mite impermeable bedding is unlikely to prove effective." Two trials stand out in this meta-analysis. Terreehorst et al. [96] investigated the effectiveness of mite-impermeable covers, classified by us as the strategy of concurrent bedroom interventions using two barriers. This large trial (n = 279) did not show clinical benefits for the treatment of rhinitis. A small trial on comprehensive exposure-based control showed benefits in the treatment of rhinitis symptom scores and total IgE [97]. In the field of eczema, Kort et al. [98] showed identical benefits to those found by Kniest et al. in a case related to storage mites by use of the exposure-based strategy. These results underline the usefulness of introducing the strategy of mite allergen control in defining meta-analysis protocols.

CONCLUSION

In summary, the clinical effectiveness of mite allergen control for the treatment of asthma is debatable [37]. It remains unclear whether the absence of evidence relates to a specific type of environmental strategy for mite allergen control, several of which were introduced in the early 1990s. A post hoc reanalysis suggests that the dominant conclusions by Gøtzsche and Johansen [37] relate to the strategy of concurrent bedroom interventions, which were mainly executed in a minimal manner. An evidence-based effectiveness assessment of the exposure-based control strategy, which is used in Western European patient practice, is still needed. Our post hoc findings indicate that future meta-analyses of mite allergen control should a priori define the environmental strategy under study. Future trials of mite allergen control are warranted to test the exposure-based strategy as well as the sparsely tested strategy of air purification.

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CHAPTER 4

Effective control of house dust mite exposure from bedding materials

van Boven FE.

Effectiveness of mite-impermeable covers: a hypothesis generating meta-analysis.
Clinical & Experimental Allergy. 2014;44(12):1473–1483.

ABSTRACT

Background

Asthma is a heterogeneous disease. The subject of mite allergen control has evolved into a debate dominated by a Cochrane review by Gøtzsche and Johansen (Cochrane Database of Systematic Reviews, 2008, Art. No: CD001187). A not well-discussed aspect of that study is the selection by those authors of a univariate meta-analysis including various interventions. This study extends the meta-analysis by Gøtzsche and Johansen and aims to generate hypotheses on the effectiveness of various bedding interventions, including the coverage of all bedding elements.

Methods

Trials were selected based on environmental criteria. The interventions were classified according to the number of barriers used. Standardized mean differences yielded the mite load, three physiological outcomes and asthma symptom scores. The influence of covariates was examined with a mixed effect model using the metafor package for meta-analysis in R.

Results

Twelve trials included 1187 observations. The interventions included one barrier or product (6 trials), two barriers or partial control (4 trials) and three barriers or integral control (2 trials). The exposure data showed considerable heterogeneity (I^2 = 93%). The risk of bias significantly (P = 0.04) influenced the final load, the square root of the interaction between the baseline load and the type of intervention as well (95% CI: -0.66 to -0.07 µg/g; P = 0.02). Changes in load showed similar tendencies. Health outcomes showed moderate to considerable heterogeneity (physiological outcomes I^2 = 44 to 94%; symptom score I^2 = 93%).

Conclusion

A meta-regression of bedding interventions indicates that integral control most significantly reduced mite load when the load was high at baseline. The number of trials was too small to allow an appropriate examination of health outcomes. Future studies are suggested to test the hypothesis that allergic patients benefit from integral control when the baseline mite load is high.

CHAPTER 5

Update on the strategy of air purification

van Boven FE, Jong NW de, Braunstahl GJ, Arends LR, Gerth van Wijk R.

Effectiveness of the air purification strategy
for the treatment of allergic asthma: a meta-analysis.
International Archives of Allergy and Immunology. 2020;181(5):395–402

ABSTRACT

Background

We updated the meta-analysis published by McDonald et al. (Chest 2002;122;1535–1542) by reviewing the effectiveness of air purification for the treatment of home-related allergic asthma (dust mite, dog, cat, and cockroach).

Methods

We analysed the trials included by McDonald et al. as well as studies published since 2000. Data on asthma symptoms scores (ASS), medication use, forced expiratory volume in 1 s as a percentage of the predicted value (FEV_1 %pred), histamine provocative concentration causing a 20% reduction in FEV_1 (PC_{20}), Asthma Quality of Life Questionnaire (AQLQ) scores, and fractional exhaled nitric oxide (FeNO) levels were extracted. The effectiveness was examined using metafor (registered in Prospero CRD42019127227).

Results

Ten trials including a total of 482 patients (baseline characteristics: mean FEV_1 %pred 83.2%, I^2 = 96.7%; mean PC_{20} 4.93 mg/mL, I^2 = 44.0%; mean AQLQ 4.67 [max. 7], I^2 = 93.7%; mean FeNO 36.5 ppb, I^2 = 0%) were included. We assessed the mean differences in the AQLQ scores as +0.36 (95% CI: 0.10 to 0.62, P = 0.01, n = 302, I^2 = 0%) and the FeNO levels as –6.67 ppb (95% CI: –10.56 to –2.77, P = 0.0008, n = 304, I^2 = 0%). The standardised mean differences in all other health outcomes were not significant (ASS –0.68, P = 0.20; medication use: –0.01, P = 0.94; FEV_1 %pred –0.11, P = 0.34; PC_{20} +0.24, P = 0.53).

Conclusion

We found statistically significant mean differences in the AQLQ scores and FeNO levels in patients with predominantly mild to moderate asthma at baseline. A large trial reported great improvement in the subgroup of patients receiving Global Initiative for Asthma step 4 therapy. We recommend that future studies on air purification focus on patients with severe and poorly controlled allergic asthma.

INTRODUCTION

Respiratory allergy is a public health problem that affects approximately 400 million people [1]. The most common home-related respiratory allergies result from house dust mite, dog, cat, and cockroach allergen (Global Initiative for Asthma, GINA, 2018). Therapies such as pharmacological treatment, immunotherapy, and avoidance of indoor allergen exposure have been developed for the treatment of allergic asthma [2]. Evidence of clinical benefits of textile-based avoidance strategies has not been demonstrated in rigorous systematic reviews [3–5]. In a scoping review, Boven et al. [6] observed potential success with the strategy of air purification for the treatment of house dust mite allergy-related asthma. Previously, McDonald et al. [7] reported improvements in asthma symptom scores (ASS) associated with air purification in a small patient subgroup (n = 88).

Whether the purification of indoor air is of clinical importance in patients with asthma remains an unanswered question. An allergic reaction is provoked in the upper airways after the deposition of aerosol particles in the epithelium. The faecal pellets of house dust mites are very small in size, at 10–40 μm (mean 22 μm), and decrease when they are partially degraded over time (diameter >0.5 μm) [8, 9]. A large proportion of cat and dog allergens are smaller than 2 μm in diameter and coagulate in the air to other aerosol dust [10]. The particle size of cockroach allergens is mainly >10 μm [11]. Industrial branches have developed specific filters (high-efficiency particulate air, HEPA, filters) that capture very small airborne particles with high efficiency (at least 85–99.999995% of particles with a diameter of 0.3 μm) [12]. These HEPA filters are applied in residential products such as housing ventilation units, mobile air cleaners, nocturnal temperature-regulated laminar airflow units, and vacuum cleaners. The strategy of air purification has a potential advantage over a textile-based control strategy because the former strategy traps airborne allergens emitted from clothes as well as emissions from indoor textiles. This advantage may explain the clinical potential of the air purification strategy. As the current evidence on the clinical effectiveness of the air purification strategy is based on small sample sizes and was obtained many years ago, there is a need to update the evidence base, as new devices for purifying the nocturnal breathing zone have been introduced [13, 14].

This study updates the existing systematic review by McDonald et al. [7] entitled "Effect of Air Filtration Systems on Asthma" by reviewing the clinical effectiveness of the air purification strategy for the treatment of home-related allergic asthma (house dust mite allergy, dog allergy, cat allergy, and cockroach allergy).

METHODS

Reference search

The starting point of this study was the systematic review by McDonald et al. [7]. This meta-analysis included ten trials. An updated search of the literature published since January 2000 was performed in EMBASE, MEDLINE, and the Cochrane Central Register of Controlled Trials (CENTRAL). The trials were limited to peer-reviewed publications in the English language, and (Congress) abstracts were excluded from the analysis. The titles and/or abstracts of the studies retrieved during the search were screened (with Endnote) by the first author (F.E.v.B.) to identify randomised trials that met the inclusion criteria outlined below. The full texts of the potentially included trials were retrieved and assessed for inclusion by the first (F.E.v.B.) and second (N.W.d.J.) authors. Any ambiguities in the selections were resolved by discussion. The inclusion criteria were as follows:

- Type of study: randomised controlled trials with blinding.
- Intervention: housing or mobile ventilation systems, including HEPA filters but not vacuum cleaners.
- Participants: participants with physician-diagnosed bronchial allergic asthma. These participants had their sensitisation assessed by either skin testing or serum assays for specific IgE antibodies (house dust mite allergy, dog allergy, cat allergy, and cockroach allergy). The asthma assessment included a history of asthma symptoms and a pulmonary function test.
- Controls: participants who received a placebo or no treatment.

Data extractions and outcomes

The data were extracted by the first author (F.E.v.B.). The trials included in McDonald et al. [7] were re-extracted, as this review presented only the results but not the extracted data. The data extractions yielded the following: characteristics of the study population including the baseline data; type of intervention and the control; study methodology, and outcomes. Missing data were requested from the study authors. A second author (N.W.d.J.) verified the selections and the data extraction conducted by the first author. Any ambiguities in the selection and the extraction were resolved by discussion.

The main outcome(s) were: the asthma symptom score; the number of patients with improved outcomes; medication use; forced expiratory volume in 1 s as a percentage of the predicted value (FEV_1 %pred); provocative concentration that causes a 20% reduction in FEV_1 (PC_{20}); Asthma Quality of Life Questionnaire (AQLQ) score, and the fractional exhaled nitric oxide (FeNO) level. Additional outcomes included: the mite allergen load from the mattress (μg/g dust); type of patient (child or adult), and the presence of primary and cosensitisation. These additional outcomes were all tested as possible explanatory variables in the presence of at least ten trials.

For the ASS, the PC20, and the AQLQ scores, the final values were extracted (following Egbewale et al. [15]). The change scores were extracted for FEV_1, medication use, and FeNO level. We defined the direction of changes as positive for an increasing FEV_1 and negative for a decreasing FeNO level and medication use.

Risk of bias (quality) assessment

The risk of bias was assessed for the following domains: sequence generation, allocation concealment, blinding, incomplete outcome data, and selective outcome reporting. The assessment was performed by the first author (F.E.v.B.) with the Review Manager (RevMan) computer program version 5.3 (the Cochrane Collaboration, 2014; Nordic Cochrane Centre, Copenhagen, Denmark). A second author (N.W.d.J.) verified the assessments of the first author by considering a sample. Any ambiguities in the assessments were resolved by discussion.

Strategy for data synthesis

The effect size was set to the standardised mean difference, excluding the number of patients showing improvement (risk ratio). We chose the mean difference as the effect size in cases in which the outcomes were all measured in the same manner (AQLQ and FeNO). First, the overall effect of the health outcomes was estimated by a random-effects meta-analysis. Additionally, the I^2 was calculated for examining heterogeneity in the outcomes. In the absence of heterogeneity ($I^2 = 0$), a fixed-effects model was used. The explanatory variables of interest included the primary sensitisation (house dust mite allergy, dog allergy, cat allergy, or cockroach allergy), the mite allergen load from the mattress at baseline, possible confounding by the type of patient (child/adult), and the presence of cosensitisation. These outcomes were analysed for a preferred minimum of ten trials per variable [16]. All the calculations were performed with the metafor package in R [17, 18]. The level of significance was set to $\alpha = 0.05$.

RESULTS

Selection of the references

We selected and included studies in two groups of publications. First, we screened the ten trials included in the meta-analysis by McDonald et al. [7]. Three trials were excluded for a lack of or only partial reporting on the treatment of asthma [19, 20] or reporting incomplete data [21]. The remaining seven trials were included in the analysis [22–28].

The second group consisted of studies identified in our updated search (Figure 1) [29]. We identified a total of 1,000 titles and abstracts. A total of 971 titles were excluded for lacking randomisation and/or blinding regarding the effectiveness of air purification.

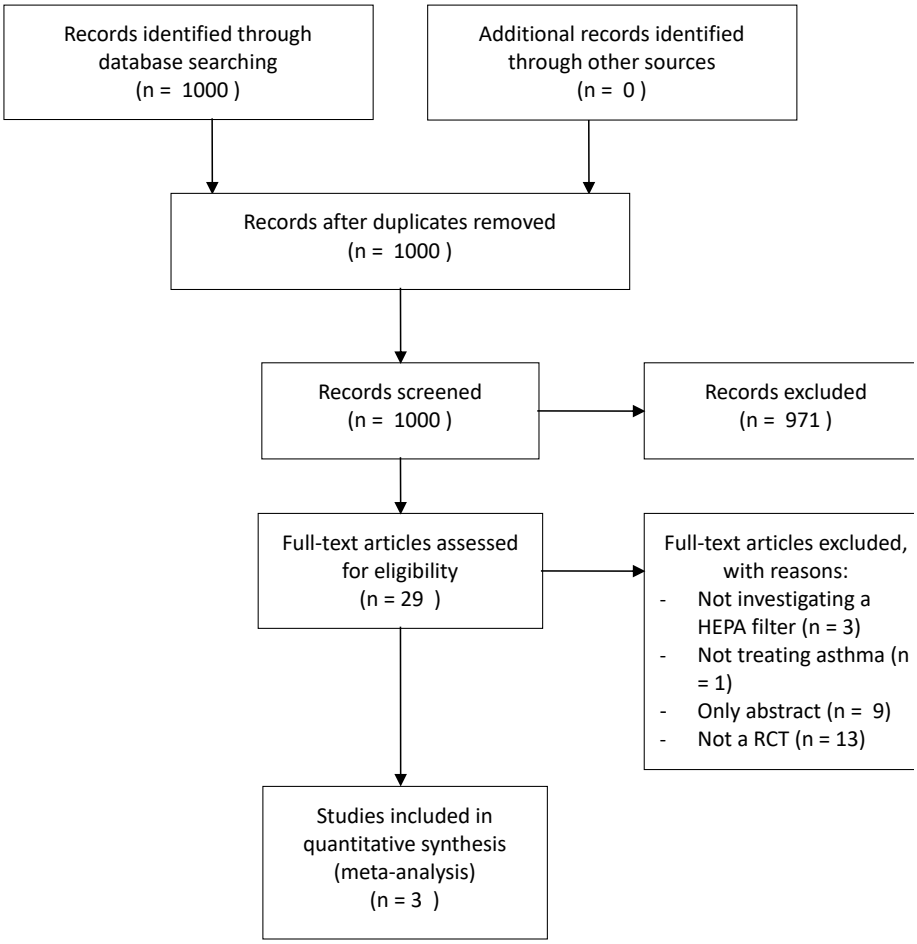

Figure 1. Flow chart of the reference search.

Twenty-nine potentially relevant titles were selected for inclusion. We excluded twenty-six full-text articles for not meeting our inclusion criteria (Appendix 2). Three full-text articles were included in the analysis [13, 30, 31]. In total, ten full-text articles were included in the meta-analysis.

Description of the trials and the baseline characteristics

Ten trials published between 1973 and 2012 reported the treatment of asthma by air purification (Table 1). In four trials, the primary sensitisation was a pet allergy [13, 27, 28, 30]; five trials reported patients with house dust mite allergy [22–26], and one trial reported a mix of primary antigens [31]. None of the trials reported monosensitisation in the included patients. One trial [31] presented data on the specific IgE during the trial. Three trials reported the treatment of children with allergic asthma; the others reported the treatment of adults or both children and adults. Four trials studied nocturnal laminar airflow in the breathing zone; the other six trials studied the use of a home ventilation or mobile device with a HEPA filter. Only one trial reported on the airborne allergen exposure [28], five other trials reported on dust exposure or allergen load at baseline [24–27, 30]. In the trial by Warburton et al. [25] only the data on FEV_1 %pred at baseline were available for analysis. In five trials, the mean FEV_1 %pred was 83.2% (I^2 = 96.7%, n = 346). The mean PC_{20} was 4.93 mg/mL (I^2 = 44.0%, 2 trials, n = 29), the mean AQLQ score was 4.67 (max. 7; I^2 = 93.7%, 2 trials, n = 304), and the mean FeNO level was 36.5 ppb (I^2 = 0%, 2 trials, n = 304). For the ASS and medication use, we had no (quantitative) data available at baseline. Ten trials reported on the use of medication at baseline. In four trials, the change in the use of medication was a primary outcome for measuring effectiveness [22, 25, 26, 28]. Two investigations instructed their patients not to change their medication [23, 27]. In two trials [13, 31], patients were allowed to use more medication. The risk of bias was judged as predominantly unclear with a low risk of bias in blinding (Figure 2).

Synthesis of the efficacy results

Four trials reported ASS as outcomes. We assessed the standardised mean difference in the ASS as –0.68 (95% CI: –2.21 to 0.85; P = 0.20; n = 77; I^2 = 51.0%; Figure 3). The standardised mean difference in medication use was –0.01 (95% CI: –0.22 to 0.21; P = 0.94; n = 401; I^2 = 0%, 4 trials; Figure 4). In three trials, the standardised mean difference in FEV_1 %pred was –0.11 (95% CI: –0.34 to 0.12; P = 0.34; n = 324; I^2 = 0%; Figure 5). Four trials reported on the PC_{20}, with a standardised mean difference of +0.24 (95% CI: –0.85 to 1.33; P = 0.53; n = 98; I^2 = 60.0%; Figure 6). The AQLQ scores were reported in two trials. We assessed the mean difference in the AQLQ scores as +0.36 (95% CI: 0.10 to 0.62, P = 0.01, n = 302, I^2 = 0%; Figure 7). This positive increase was strongly influenced by the large trial by Boyle et al. [31] (weight 77%). The mean difference in the FeNO level

was –6.67 ppb (95% CI: –10.56 to –2.77, P = 0.008, n = 304, I^2 = 0%; Figure 8). None of the included trials reported on whether the physician-diagnosed numbers improved. Overall, the number of trials available was too small to allow any subgroup analysis.

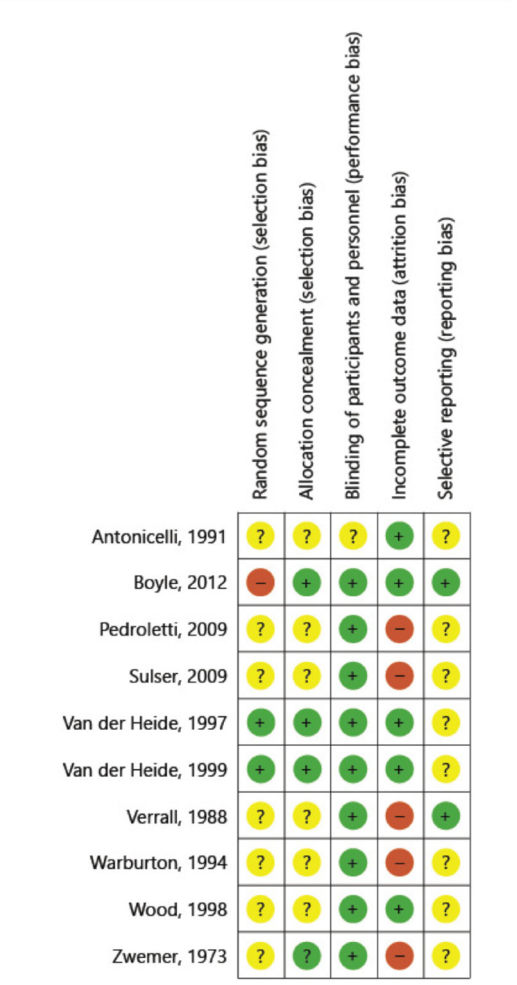

Figure 2. Summary of the judgements on the risk of bias in the trials.

Table 1. Characteristics of the included studies

Trial	Use of a HEPA filter	Subjects	Primary allergy	Health outcomes extracted
Zwemer [22], 1973	Nocturnal laminar airflow	Child	House dust mite	ASS
Verrall [23], 1988	Nocturnal laminar airflow	Adult	House dust mite	Medication use
Antonicelli [24], 1991	Mobile device	Adult	House dust mite	ASS, medication use, FEV_1 %pred., PC_{20}
Warburton [25], 1994	Mobile device	Adult	House dust mite	FEV_1 %pred.
Van der Heide [26], 1997	Mobile device	Adult	House dust mite	PC_{20}
Wood [27], 1998	Mobile device	Adult	Cat	ASS, medication use
Van der Heide [28], 1999	Mobile device	Child	Cat or dog	Medication use, PC_{20}
Pedroletti [13], 2009	Nocturnal laminar airflow	Adult	Cat or dog	AQLQ score, FeNO level
Sulser [30], 2009	Mobile device	Adult	Cat or dog	PC_{20}
Boyle [31], 2012	Nocturnal laminar airflow	Adult	House dust mite or cat	Medication use, FEV_1 %pred., AQLQ score, FeNO level

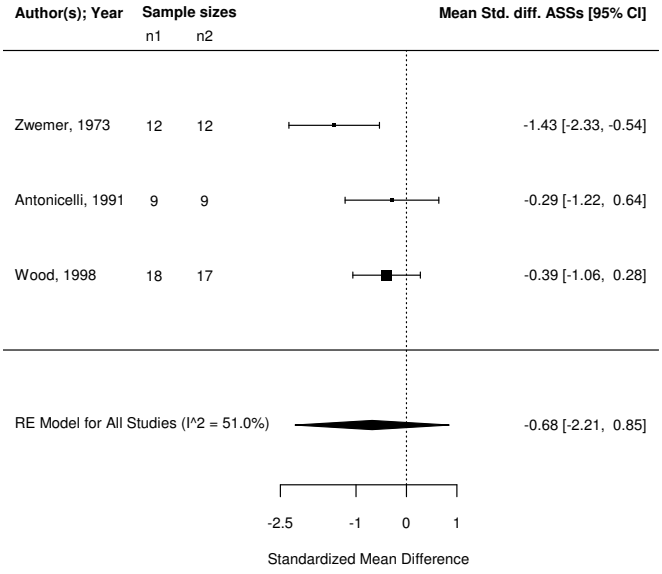

Figure 3. Forest plot of the standardised mean differences in the ASS.

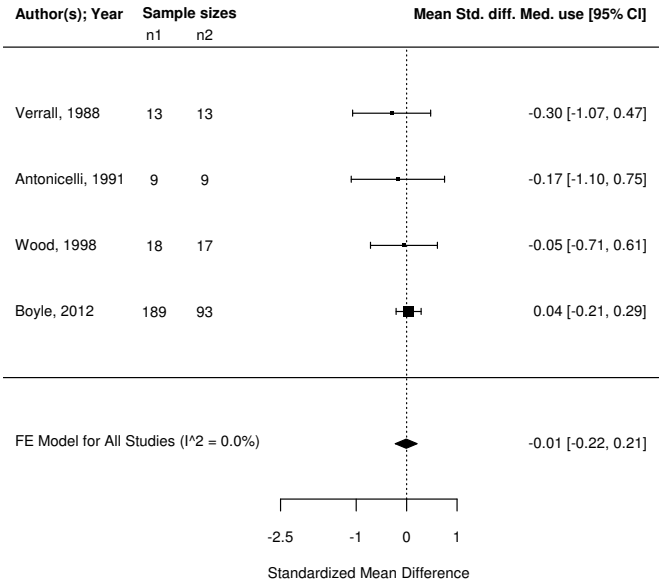

Figure 4. Forest plot of the standardised mean differences in medication use.

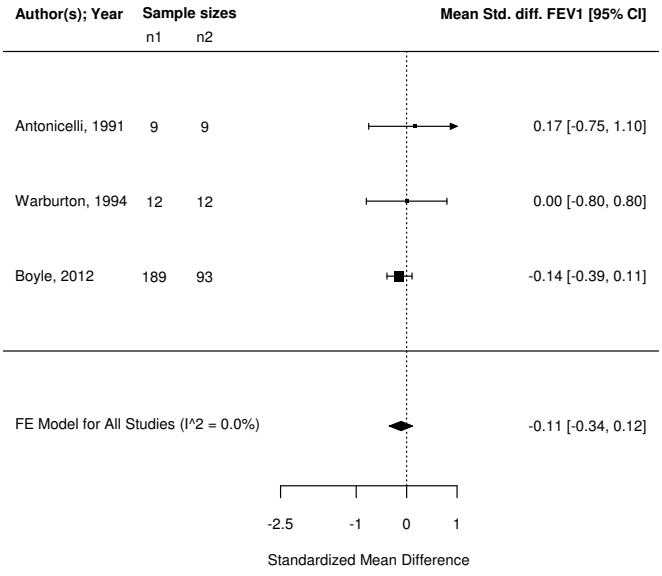

Figure 5. Forest plot of the standardised mean differences in the FEV1 %pred.

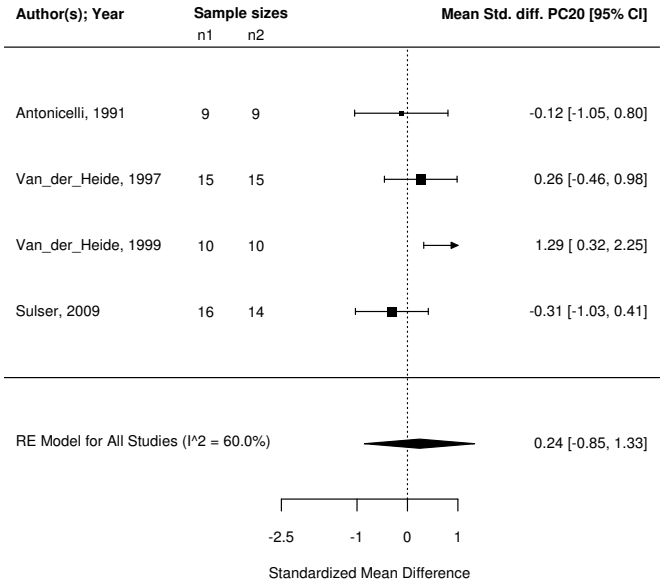

Figure 6. Forest plot of the standardised mean differences in the PC20.

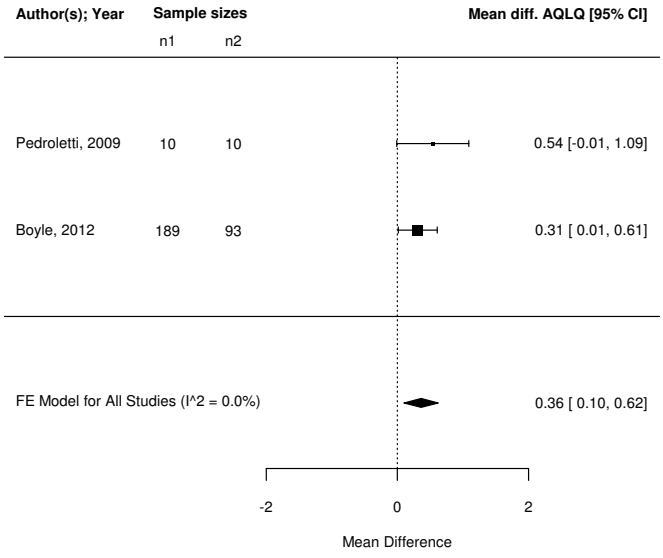

Figure 7. Forest plot of the mean differences in the AQLQ scores.

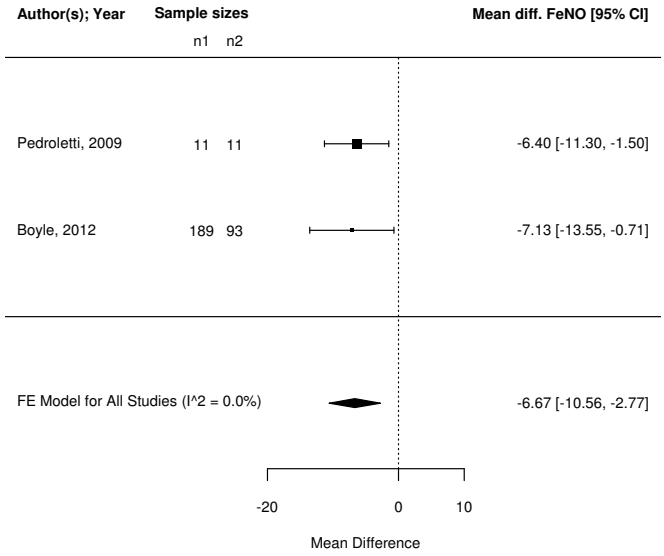

Figure 8. Forest plot of the mean differences in the FeNO levels.

DISCUSSION

We reviewed the clinical effectiveness of the air purification strategy for the treatment of home-related allergic asthma in ten trials. The mean differences in the AQLQ score (MD = +0.36; P = 0.01) and the FeNO level (MD = –6.67; P = 0.008) were statistically significant, suggesting that asthma patients may benefit from air purification. These results were obtained in patients with predominantly mild to moderate asthma outcomes at baseline (the FEV_1 %pred, the AQLQ score, and the FeNO level). The overall airway hyperresponsiveness was mild at baseline, according to the classification by Cockcroft et al. [32]. The risk of bias in the trials was predominantly judged unclear; however, blinding has a low risk of bias.

The strength of this meta-analysis was the rigorous selection of trials and extraction of data. We decided a priori whether to extract change or final values considering the statistical notes by Egbewale et al.[15]. In our study, we excluded some trials that were included by McDonald et al. [7] due to a critical process in extracting the data. For instance, they included the ASS by Reisman et al. [20]. After a critical review of this paper, we decided not to extract these data as only 11 of 32 patients were diagnosed with asthma; thus, we excluded this trial from the analysis. We noticed that this trial was also excluded for the same reason in the meta-analysis by Gøtzsche and Johansen [3]. While the previously analysed trials were quite old, the recent trials included the use of validated

outcomes such as the AQLQ score [33]. In patients with mild to moderate disease, we observed small (not reaching the minimum clinically important difference) but significant improvements in the AQLQ scores and FeNO levels. This effect could possibly be stronger in patients with severe asthma than in those with mild to moderate asthma. This possible tendency is well presented in the large trial by Boyle et al. [31]. They studied the effectiveness of the Protexo system (a nocturnal temperature-controlled laminar airflow) and reported the outcomes of the use of medication, FEV_1 %pred, AQLQ scores, and FeNO levels. They differentiated the AQLQ score, their primary outcome, and the asthma status defined by the treatment intensity of GINA and the asthma control test (ACT). After a 1-year treatment period, Boyle et al. [31] reported an AQLQ score difference of +0.31 (P = 0.04) in all the studied patients (n = 282). When limited to the patients classified as requiring GINA step 4 therapy (GINA 4) at baseline, the difference became +0.47 (P = 0.04, n = 129). In the patients receiving GINA 4 with poor control (ACT <18), the difference in the AQLQ score was +0.70 (P = 0.02, n = 87). Additionally, in the patients with a high FeNO level at baseline, the same tendency was reported by Boyle et al. [31] (mean difference in FeNO –29.7 ppb, P = 0.001).

The limitation of this meta-analysis was the relatively small number of trials included in the analysis. Our update did not result in many new included trials. In total, we included the same number of trials (n = 10) as McDonald et al. [7] included in their earlier meta-analysis. We had to exclude three trials that were included by McDonald et al. [7] because of a lack of reporting on the treatment of asthma or incompleteness of the data. McDonald et al. [7] previously reported "a small but statistically significant difference in total symptoms associated with use of domestic air filters." They did not find benefits associated with medication use or morning peak flow values. In our update, we did not find a significant difference for the ASS outcome. The significance reported by McDonald et al. [7] was based on an analysis by the fixed-effects model. As the ASS showed moderate heterogeneity (I^2 = 51%), we introduced the random-effects model and the significance was lost. The use of domestic HEPA filters will also be of relevance in the treatment of non-allergic asthma, for instance by filtering indoor air pollution. As we included only trials on the treatment of allergic asthma, this possible issue did not bias our results. The description of the allergen exposure differed in the trials and was sometimes poorly presented. Therefore, we could not analyse the degree of the exposure, and also cannot exclude the possibility that a variation of allergens from other sources affected the results.

The significant differences we found were both a result of trials sponsored by Airsonett AB (Angelholm, Sweden). One of these trials [31] was predominantly responsible for the positive AQLQ score analysis and was judged as having a risk of bias in randomisation. Their treatment group was twice the size of the control group. In principle, this creates a risk of selection bias as recruiters could "guess with greater than a 50% probability what

the next treatment allocation will be" [34]. In their report, we did not find indications for baseline imbalances biasing the estimates. Another issue of relevance in both trials on the Protexo system is the possibility of changes in medication use. Pedroletti et al. [13] reported that "inhaled, short-acting beta-2 agonists were allowed as rescue treatment." Boyle et al. [31] instructed that the patients "asthma medication were kept unchanged for the first 3 months, and thereafter adjusted to optimise asthma control." We cannot exclude the possibility that these instructions confounded the significant results we found. Overall, the results require independent repeating, with careful monitoring of allergen exposure.

Other studies on the Protexo system resulted in (some) clinical benefits. Schauer et al. [35] observed reduced asthma exacerbation and hospitalisations in an observational study in patients with predominantly difficult-to-control asthma. In a recent pilot study, Gore et al. [36] reported the potential for the use of the Protexo system as an add-on to standard pharmacological treatment in children with difficult-to-control atopic dermatitis. These results also reflect the need to study patients with severe and uncontrolled conditions.

In brief, we reviewed the clinical effectiveness of the air purification strategy for the treatment of home-related allergic asthma (house dust mite allergy, dog allergy, cat allergy, and cockroach allergy). We found statistically significant mean differences in the AQLQ scores and FeNO levels in patients with predominantly mild to moderate asthma at baseline. A large underlying trial [31] showed potentially great improvement in the AQLQ scores in the subgroup of patients receiving GINA 4 therapy with poor control. Future studies on air purification strategies with rigorous trial designs that focus on patients with severe and poorly controlled allergic asthma are warranted.

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CHAPTER 6

Exploring novel strategies in the control of house dust mites

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House dust mites and altitude. In: T. White (ed). Termites and mites;
Distribution patterns, biological importance and ecological impacts.
Nova Science Publishers, Inc. 2015, New York, p.75-90, ISBN: 978-1-63484-007-1
(with permission from Nova Science Publishers, Inc.)

ABSTRACT

Background

House dust mites in Europe are dramatically reduced at high altitude (> 1500 m) because the micro humidity is too low to support the survival of mite populations. At high altitude, barometric pressure, oxygen content, outdoor temperature, and absolute outdoor humidity decrease. From an environmental viewpoint, it is not well discussed which physical phenomenon causes the absence of mites at high altitudes in Europe. The aim of this study was to systematically review the relationship between mite allergen exposure in Europe and altitude-related characteristics using existing data subsets.

Methods

Data were collected on mite allergen exposure at different altitudes in Europe from three earlier studies. For all locations, the oxygen percentage, the mean outdoor temperature in January and the barometric pressure were estimated. The mean mite allergen exposure rate for mattresses was set to the allergen load in Der 1 from mattresses or the mean number of mites divided by 50 for mattresses and 5 for carpets. The standard deviation of the exposure rate was calculated by imputation. Collinearity between altitude characteristics was tested with the condition number test. The relationship between the exposure rate and altitudinal characteristics was examined with a mixed effects model with the package metafor in R (version 3.1.2).

Results

Data from 35 sampling localities covered 4017 observations on mite abundance throughout Europe. The exposure rate varied from 0.01 to 36 μg/g dust, with a median of 1.05 μg/g dust, and showed considerable heterogeneity ($Q = 3080$; $P < 0.0001$; d.f. = 34). The condition number φ ranged from 1.5 (oxygen percentage versus outdoor temperature) to 54.5 (oxygen percentage versus barometric pressure), indicating collinearity between the latter two variables. With regards to the subset analysed, the mixed effect models significantly explained the exposure rate using multiple variables related to altitude.

Conclusion

The results of this observational meta-regression on house dust mite exposure in Europe support earlier findings on the limiting effect of dry climates. Additionally, house dust mite allergen exposure around the European Alps showed an association with thin air at elevated altitude. These findings suggest future studies to test the hypothesis that multiple altitudinal characteristics including thin air limit house dust mite exposure in European Alps and urge for an experimental validation on house dust mite physiology at high altitude.

CHAPTER 7

The description of house dust mite aeroallergen measurement results

van Boven FE, Jong NW de, Loomans MGLC, Braunstahl GJ,
Gerth van Wijk R, Arends LR.

Describing indoor house dust mite aeroallergen exposure: Inclusion of peak concentrations. European Aerosol Conference - EAC 2020 (abstract accepted)

ABSTRACT

Background

Measuring house dust mite aeroallergen concentrations is essential in understanding mite allergen exposure. We studied the statistical ways of summarizing measurements of fluctuating mite aeroallergen exposure inside homes.

Methods

To study emissions from beddings, we measured the time-related airborne dust concentration after shaking a duvet. Analysis was performed both by a method based on the estimated mean and by a non-linear model.

Results

In a sample of twenty-eight studies, all of them reported a sum of concentrations; only one also reported the peak concentration. This peak concentration was four times higher than the mean. In our four experiments on shaking a duvet (245 to 275 measurements each), the peak value was two to four times higher than the mean. The mean-based and non-linear models both predicted the sum of concentrations exactly. A 1% upper prediction bound and the non-linear model predicted the peak emission rate moderately well (64 to 92%, and 63 to 93%, respectively).

Conclusion

Mean levels of mite aeroallergen measurements differ substantially from peak concentrations. The use of the mean is only sufficient to predict the sum of concentrations. We suggest that, mite aeroallergen measurements should include information on the peak as well as the mean.

INTRODUCTION

Measuring house dust mite aeroallergen concentrations is essential in understanding personal mite allergen exposure [1]. The species of the mites *Dermatophagoides, pteronyssinus, Dermatophagoides farinae*, *Euroglyphus maynei*, as well as the specie *Blomia tropicalis*, are important domestic sources of house dust mite allergens, which are found mainly in their faecal products [2,3]. The spherical faecal particles, with diameters of 10–40 μm [4], partially degrade with time into smaller fragments of 1–10 μm [5], which easily become airborne. Most large airborne mite allergens settle rapidly in five to twenty minutes after emission [6]. Environmentally, indoor exposure is characterized by the peak concentration (the largest amount of mite aeroallergen that a person is exposed to at any one time) and the sum of concentrations (the total amount of mite aeroallergen that a person is exposed to during a specified time) [7,8]. In daily life, patients are exposed in their homes to repeated environmental allergen emissions, followed by decays [4]. In the field of aerobiology, such diurnal fluctuating exposure is modelled with a tailored model, such as a time series or periodic function [9].

Methods for the measurement of airborne house dust mite particles during specific portions of the day or night, e.g. during sleep, have also been proposed [10]. Historically, experiments on exposure to indoor mite aeroallergens expressed variation in terms of either the mean concentrations during disturbed conditions or the mean concentrations during undisturbed conditions [4,11,12]. Sampling periods started from 20 minutes duration. Decades later, modern techniques show that fluctuations in indoor particle exposure take seconds to a minute [13]. However, from a statistical point of view, a not well-discussed topic is whether the use of mean concentrations can be improved by presenting more information on the peaks. Allergen levels for all particle sizes are very well correlated ($R^2 \geq 0.92$) with aerosol dust exposure [14]. This creates the possibility for using real-time aerosol dust exposure measurements as a proxy for observing these fluctuations.

The aim of this study is to examine how dust mite allergen exposure levels inside homes statistically have been reported in the past, and then, to enquire into whether the commonest methods of reportage are indeed the best. Accordingly, we first search and summarize the literature on statistics of indoor aeroallergens measurements inside homes, and then experimentally study emission from bedding, paying special attention to the mean concentration, peak concentration, and sum of concentrations and using the methods of applied statistics.

METHODS

Summary of literature

A sample from the literature on indoor measurement of airborne mite-allergen exposure was selected from Pubmed and Web of Science by use of the keyword search-strings 'airborne AND mite AND (allerg* OR antigen* OR exposure)' and 'aeroallergen AND mite AND sampl*'. We searched for all references up to August 9th, 2019. The results were limited to those articles referring to measurements of airborne mite-allergen concentration inside homes and written in the English language. References were selected on the basis of their abstracts. We also screened for descriptions of the measurements as well as details of the indoor environment. Data were extracted for the airborne concentrations, the measuring periods, and the particle size distribution. The procedure is illustrated in Figure 1 [15]. For this summary of statistics from the literature, we focussed on three characteristics of exposure: the mean concentration during undisturbed conditions, the mean concentration during disturbed conditions, and the peak concentration. The mean is defined as "the arithmetic average of the observations" [16]. Thus, the mean-value can differ depending on measuring during various types of human activity: for instance, when measuring both under disturbed and undisturbed conditions. Only articles were included reporting time-related statistics or statistics categorized to different indoor conditions.

Pilot study

In order to study the emissions from a bedding site, we measured the airborne dust levels in a bedroom of each of two Dutch family homes after shaking a duvet vigorously once or twice. One duvet was 16 years old, the other 4 years old. Both bedrooms were unheated and unused, with all ventilation devices off and the windows closed. Every six seconds, counts of particles in the size-range 0.25 to 32 μm were collected by an aerosol spectrometer (Grimm 1.109). Extractions from the datasets were confined to the period of mechanical activation of the duvet. Only data from the coarse fractions (particle diameters >2 μm) were used. A recent study has shown that large particles (>6 μm) tend to be deposited mainly in the upper airway, whereas particles in the size range 2–6 μm are deposited in the central and small airways [17]. In another study, Brown et al. observed that effectively all particles ≤1 μm penetrate (or pass) the extra-thoracic region as well as the tracheobronchial region [18]. These results indicate that particle sizes ≤ 1 μm are not of relevance in allergic asthma.

Total mass concentrations were obtained from the particle counts (assuming the particles to be made of material with a density of 1 g/cm^3). We assessed the peak concentration and the sum of concentrations using of two approaches. The first method yielded an estimated mean for predicting the sum of concentrations, from which we

derived a 1% upper prediction bound $Y_{0.99} = \overline{Y} + t_{0.01;n-1} * S * \sqrt{(1+1/n)}$ for predicting the peak concentration ($Y_{0.99}$ is the 1% upper prediction bound; $\overline{Y}$ is the estimated mean; t is the t-value; S is the standard deviation; n is the sample size). The second method used a nonlinear model $Y_t = \beta_0 + \beta_1 * \exp(-\beta_2 * t)$ [8], where t is the time in seconds; Y_t is the concentration at time t; β_0 is a parameter representing the background concentration; β_1 is a parameter representing the concentration at t = 0 s; and β_2 is a parameter representing the decay or settling rate of the dust concentration. We assessed the quality of the fit by the coefficient of determination R^2. A sensitivity-analysis yielded the fitting for the first ten minutes after activation of the duvet. All calculations were performed in R, version 3.4.1 [19]. The package minpack.lm was used for estimating the nonlinear model.

RESULTS

Literature search

We found 610 references related to the measurement of airborne house dust mite allergen concentration, of which 81 appeared to be duplicated (Figure 1). Fifty-seven full articles were selected for screening descriptions of the measurements. Twenty-eight studies reported on measurements of airborne dust mite exposure in the home environment. All of these summarized the measurements by use of the mean. Ten of these studies presented time-related results on indoor exposure, for instance after changing the bedding (Table 1; Refs. 4,6,10,12,20-25). Five studies used a volumetric air sampler [4,6,10,12,23], and one used an ionic sampler [20]. The other four studies used an intranasal sampler [21,22] or a personal sampler [24,25]. The mean concentrations during undisturbed conditions ranged from 0 to 1.7 ng allergen/m^3, and the mean concentration during disturbed conditions ranged from 0.3 to 190 ng allergen /m^3. These measurements were presented in various units (Der p1, allergen, protein).

Only one study [6] presented a peak concentration (736 ng house dust mite allergen / m^3 after 5 min) rather than a mean. This study is particularly interesting because their measurements began with the changing and vigorous shaking of the bedding while measuring, and ran for 24 h. Mite antigen concentration (protein) was measured in five different particle sizes (<0.8 μm; 0.8–1.4 μm; 1.4–2.3 μm; 2.3–4.1 μm; >4.1 μm) after sampling for 5 min, 20 min, and 24 h. The concentration measured was 100% at 5 min, 34.1% after 20 min, and 0.2% after 24 h. Also, other studies showed large differences between disturbed and undisturbed conditions. For instance, De Blay et al. [12] reported a ratio > 200 between both conditions, indicating a rapid settling of particles.

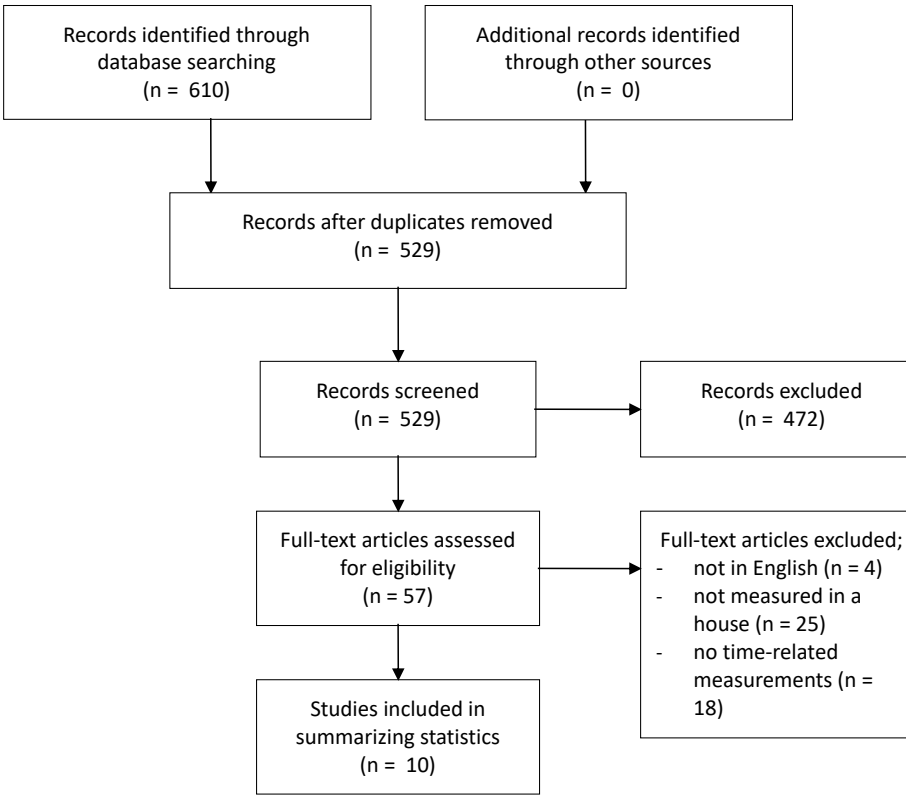

Figure 1. PRISMA Flow chart of the literature search.

Pilot study

The four experiments began with shaking a duvet one or two times. In each experiment, 245 to 275 measurements were made. The sum of concentrations in the experiments was 1337 to 7083 ng/dm^3 dust, compared to an initial concentration of 19.5 to 54.0 ng/dm^3. The older duvet (16 years) caused a higher initial exposure than the younger duvet (4 years). We achieved a perfect prediction (100%) of the sum of concentrations by both the estimated-mean method and the non-linear model for all four experiments. The percentage predicted initial concentration ranged from 64 to 92% (1% of the upper prediction bound), and 63 to 93% (nonlinear model) (table 2). The coefficient of determination R^2 for the four experiments was 0.09; 0.07; 0.05; 0.03 (use of the mean) and 0.85; 0.85; 0.86; 0.93 (nonlinear model). (Figure 2-5).

In a sensitivity analysis, we limited the data to the first ten minutes after activation of the duvet and found that the percentage predicted initial concentration ranged from 79 to 105% (1% of the upper prediction bound), and 88 to 106% (nonlinear model).

Table 1. Summary of house dust mite aeroallergen measurements and statistical analyses in selected studies

Study	Sampling device	Activity	n	Mean exposure / concentration during undisturbed conditions (duration)	Mean exposure / concentration during disturbed conditions (duration)	Peak exposure / concentration (duration)
Blay, 1991 [12]	Cassella Mark II cascade impactor.	Vacuum cleaning.	7	< 0.3 ng/m^3 in group I and II mite allergen (20–120 min)	68 ng/m^3 in group I and 25 ng/m^3 in group II (20–120 min)	NA
Curtis, 2003 [20]	Ionic Breeze Quadra (an ion-charging device).	Normal domestic activities ("normal" not specified).	44	< 0.01 ng/m^3 in group I mite allergen (120 min)	+/- 20 ng/m^3 in group I mite allergen (45 min)	NA
Gore, 2002 [21]	Intranasal air samplers.	Lying in bed.	12	3 halo counts for Der p1 + Der p2 (30 min)	79 halo counts for Der p1 + Der p2 (30 min)	NA
Poulos, 1999 [22]	Intranasal air samplers.	Domestic activities, including lying in bed.	2	0 particles containing Der p1 (10 min)	9 to 10 particles containing Der p1 (10 min)	NA
Sakaguchi, 1989 [23]	Portable air-sampler (KI-636 Dylec)	Disturbed conditions in the bedroom, including bedmaking	10	0.03 Der p1 ng/m^3 (109-124 h)	30.9 Der p1 ng/m^3 (40 min)	NA
Sakaguchi, 1992 [10]	Portable air-sampler (KI-636 Dylec)	During sleep without the disturbance of the bedmaking	6	0.01 Der p1 ng/m^3 (4.9 – 9.3 h)	0.22 Der p1 ng/m^3 (4.9 – 9.3 h)	NA
Swanson, 1985 [6]	Air-Sentinel.	Changing and shaking of the bedding.	1	1.7 ng protein/m^3 (24 h)	189.9 ng protein/m^3 (20 min)	736.1 ng protein/m^3 (5 min)
Tovey, 1981 [4]	Anderson filter holder connected to a vacuum pump.	Domestic activities.	13	< 0.3 ng Der p1 (120 min)	< 0.3 to 30 ng Der p1 (45 min)	NA
Tovey, 2013 [24]	A portable air-pump carried on the shoulder.	Domestic activities and in-transit activities.	12	0.05 ng/m^3 (8 h)	1.12 ng/m^3 (120 min)	NA
Tovey, 2016 [25]	A small impaction collector worn on the shoulder.	Domestic activities and in-transit activities.	10	0.02 ng/m^3 (27 min)	0.09 ng/m^3 (7.3 h)	NA

NA = not applicable. N = sample size

Table 2. Predictions of the peak concentration measured from shaking a duvet (duration of measurement six seconds)

Experiment *	Shaking of the duvet (age of the duvet)	Initial or peak concentration (ng/dm³)	1% upper prediction bound (ng/dm³)	Prediction by non-linear model (ng/dm³)
1	One time (4 years)	19.5	12.6	12.3
2	Two times (4 years)	21.5	14.3	16.7
3	One time (16 years)	31.9	26.4	23.6
4	Two times (16 years)	54.0	49.6	50.3

* Experiment 1-4 shown in figure 2-5.

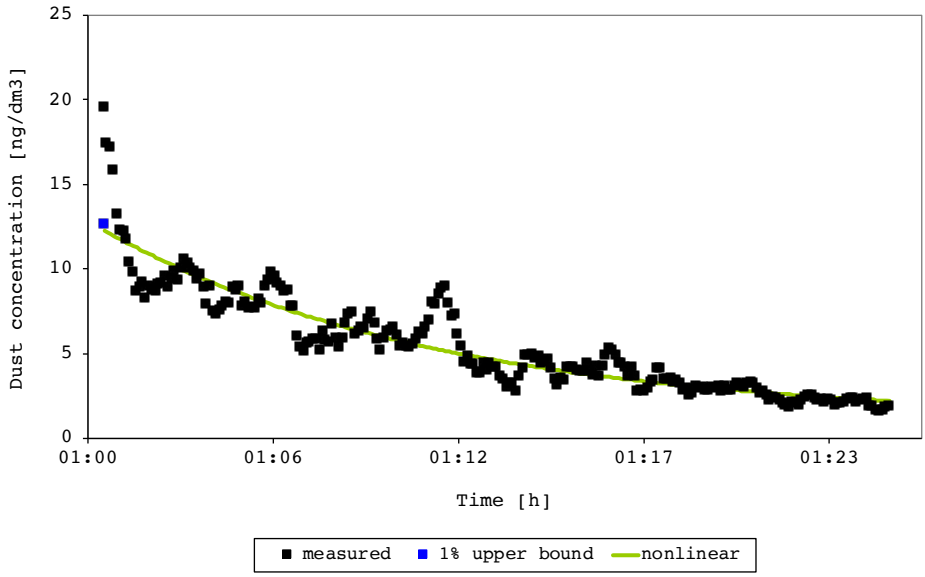

Figure 2. Measured and predicted dust concentration in experiment 1 after shaking a four-year-old duvet one time.

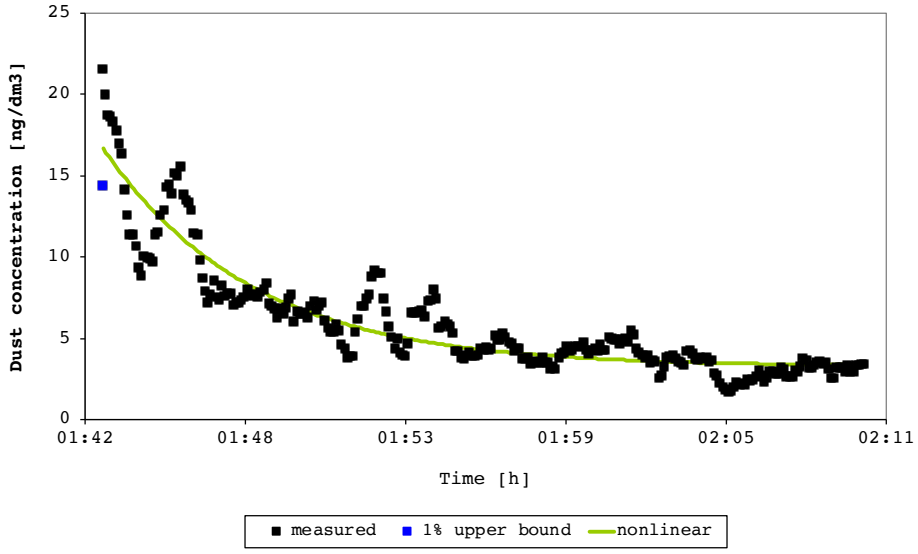

Figure 3. Measured and predicted dust concentration in experiment 2 after shaking a four- year-old duvet two times.

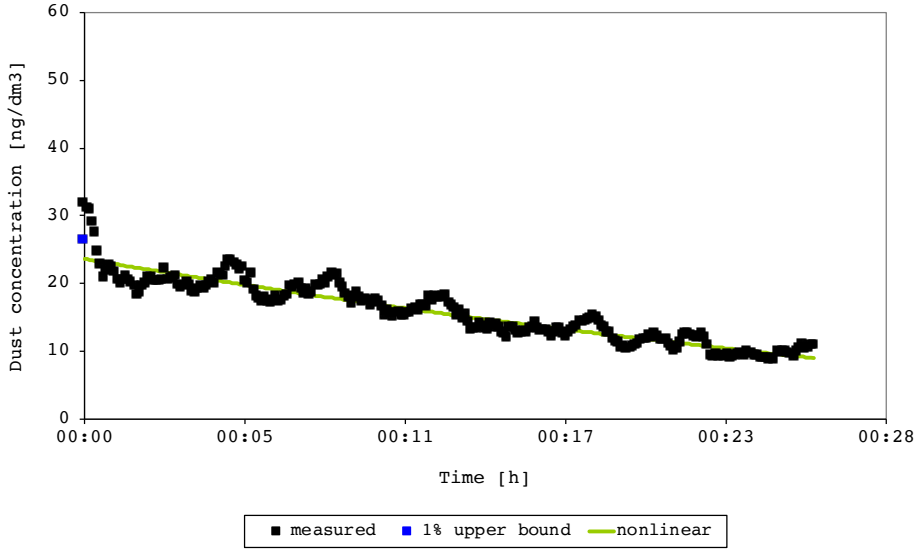

Figure 4. Measured and predicted dust concentration in experiment 3 after shaking a sixteen-year-old duvet one time.

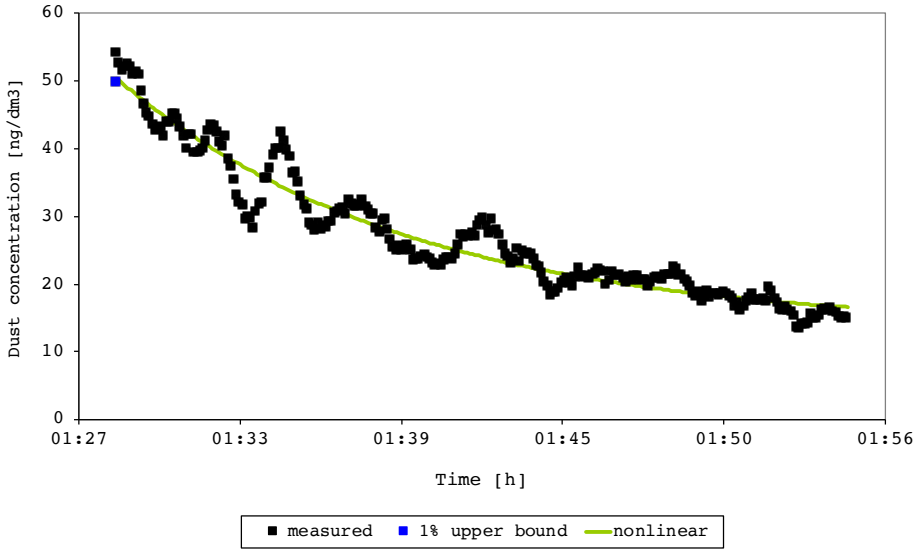

Figure 5. Measured and predicted dust concentration in experiment 4 after shaking a sixteen-year-old duvet two times.

DISCUSSION

Measurement of personal mite aeroallergen exposure is complex. Early studies showed that human activities increased the mean aeroallergen levels [4,11,12]. The last development is the use of a small sampler, worn on the human body [25]. We investigated the way of describing the measurement of fluctuating indoor mite aeroallergen concentrations from beddings.

A sample of fifty-seven articles on indoor measurements of airborne mite allergen exposure was taken from the literature. Only measurements in houses were considered. All articles summarized their results by the use of the mean (the arithmetic average of the observations), which is also sufficient to describe the sum of concentrations. Ten studies reported time-related indoor measurements, all including a mean during disturbed conditions and a mean during undisturbed conditions. A recent study on indoor aerosol dust particles suggests to measure fluctuations occurring during the disturbed and undisturbed conditions [13]. This is supported by the experiment by Swanson et al. [6], who showed relative differences of a ratio of 110 between disturbed and undisturbed conditions.

The peak concentrations measured by Swanson et al. [6] was four times higher than the mean of 20 minutes measurement. These results should be interpreted with caution, as the assays used by Swanson et al. [6] might vary considerably. In our experiments also,

peak values differed substantially from mean levels. Considering the differences between the measured emissions in our four experiments, shaking a duvet once or twice is not an easily reproducible disturbance. Again, however, the relative change was of importance in this case. Generally, the nonlinear model and a 1% upper bound predicted the peak level best when the variation in background exposure was low. Our data showed large fluctuations in the background levels, dominating the predicted decay after an emission, and reducing the quality of fit, especially for the nonlinear model. These large fluctuations can perhaps be explained by a heterogeneous distribution of the particles in the indoor air after the moment of emission. In general, the non-linear model fitted the data best ($R^2 \geq 0.85$ for data with large fluctuations). This fit improves when limiting the data to the first 10 minutes of measurement. However, the aim of our study was not necessarily to find the best predictive model, but rather the best way of describing the variation in the mite aeroallergen exposure.

The strength of this study is that, to our knowledge, this is the first study of how statistical principles should be applied to presenting results on airborne mite-allergen concentrations in combined disturbed and undisturbed conditions. Our pilot study showed tendencies consistent with the relative amounts found in the early experiment by Swanson et al. [6], indicating that the use of the mean alone is not sufficient to describe the fluctuating mite aeroallergen concentration from bedding. Multiple statistical models are available, like time series, a periodic function and regression [8,9]. Nevertheless, the wide ranges in reported results suggest that much more study of personal exposure is needed.

A major limitation of this study relates to the clinical implication. Clinically, it is clear that the increased allergen concentrations play a role in asthma symptoms [26]. However, it has yet to be confirmed whether asthma outcomes correlate with peak concentrations of house dust mite allergens. Laboratory experiments that have been performed on the relation between asthma outcomes and mite aeroallergen doses were mostly based on a homogeneous mite airborne dose [27-29]. Field studies in humans relating personal airborne mite-allergen levels to clinical symptoms of asthma are sparse. In 1996, Custovic et al. [30] performed a study on the correlation between domestic mite allergen exposure and asthma severity in 53 patients during sleep. The overwhelming majority (94%) of mean airborne observations during the night were under the lower limit of detection for the allergen assay. Correlations were described between the allergen load and several asthma outcomes. While all the correlations were statistically significant, their magnitudes were all moderate ($R^2 = 0.38$ to 0.49). These results show that more research is needed to understand the relationship between exposure and clinical outcomes. The use of tailored statistics combined with respiratory characteristics (e.g. FEV_1/FVC), may allow the assessment of the actual aerosol exposure in the human airways, and provide evidence for the causal relation between house dust mite allergen exposure and allergic asthma in atopic patients.

In conclusion, measurements of indoor mite aeroallergen concentrations are commonly summarized by the mean. A recent study favours the use of peak exposure during disturbed conditions [13], calling for the use of other statistics than only the mean. We suggest that future studies describing mite aeroallergen measurements include information on the peak concentration as well as the mean. The measurements should be conducted with state of the art assay technology and more sophisticated mathematical models, such as regression or a time series analysis, should be used in the analysis.

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CHAPTER 8

General discussion

INTRODUCTION

Indoor allergen-related asthma is a variable disease of the lower conducting airways, affecting several million people worldwide [1]. In general, the management of the allergic reaction involves the control of the exposure and/or the immunologic reaction [2]. The initial medical interventions accepted in the treatment of allergic asthma in the Netherlands involved exposure avoidance by removing patients to an apparently allergen-proof chamber [3], or a compatible sojourn in a Swiss alpine house with a dust mite-free environment [4]. Modern trials tested the clinical benefits of avoidance in randomized blinded experiments, resulting in an absence of evidence [5]. The debate on environmental means reached an impasse [6]. Meanwhile, the method of measuring personal exposure was developed, which assessed the airborne allergen concentration a person is exposed to at any point [7]. This novel approach showed that the site of highest allergen exposure varies for patients [8]. Personalized exposure was denoted as a possible explanation for the impasse on effectiveness [9]. However, this did not alter the state of evidence [10]. A question yet unaddressed is whether exploring the variance in asthmatic patients, their homes, the types of interventions, and possible new strategies for control, could restart the debate.

In this thesis, we systematically reviewed whether patients with allergic asthma benefit from environmental means of avoidance, with regard to the type of patient and differences in exposure, the strategy of choice, and the types of interventions, with a focus on house dust mite allergy-related asthma. Specific topics allow the exploration of oxygen content as a factor limiting dust mite survival and the description of personalized allergen exposure.

FINDINGS

Baseline characteristics in trials

Our study commences by addressing the Cochrane review on house dust mite control by Gøtzsche and Johansen [10]. This meta-analysis currently summarizes the effectiveness of 55 trials on house dust mite control for the treatment of asthma. The baseline characteristics of the trials investigated by Gøtzsche and Johansen [10] varied. We observed a mean house dust mite allergen load of 9.86 μg/g from the mattress of (95% CI: 5.66 to 14.05 μg/g dust), a mean standardized asthma symptoms score (ASS) of 0.13 (95% CI: 0.08 to 0.18), a mean forced expiratory volume in 1 s percentage of predicted (%) (FEV_1 %pred.) of 85.3% (95% CI: 80.5 to 90.1%), and a mean histamine or methacholine concentration that causes a 20% reduction in the FEV_1 (PC_{20}) of 1.69 mg/mL (95% CI: 0.86 to 2.52 mg/mL). These levels suggest that several clinical trials included patients with rather mild to moderate asthma who were exposed to varying and, at times,

negligible levels of house dust mite allergen load. The moderate asthma outcomes were most likely modified by the use of asthma medication, reducing the scope for improvement in the trials (**chapter 2**), owing to which, no or negligible improvements were anticipated. The baseline characteristics suggest to investigate patients with more severe and uncontrolled asthmatic conditions during their exposure to high levels of house dust mite allergen. In our data, we only observed one trial [11] that reported this combination of patients with a severe outcome (bronchial hyper-responsiveness PC_{20} < 1.0 mg/mL) during exposure to a high allergen load (mean 16.0 µg/g dust). Ehnert et al. [11] reported a standardized mean difference in PC_{20} of + 1.19 (95% CI: 0.12 to 2.25; P = 0.03; n = 16; figure 1) after 12 months by treating asthmatic children using concurrent bedroom interventions (use of two barriers).

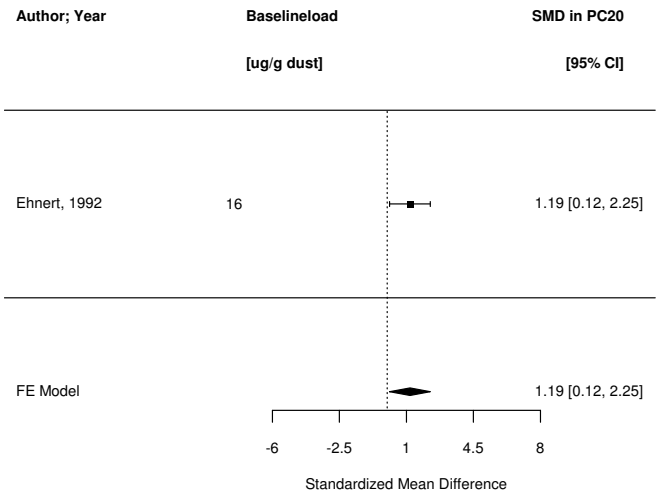

Figure 1. Standardized mean difference in PC_{20} after 12 months in 16 children with a bronchial hyper-responsiveness of PC_{20} < 1.0 mg/mL while exposed to a high allergen load at baseline (mean 16.0 µg/g dust) as reported by Ehnert et al. [11] using concurrent bedroom interventions (use of two barriers)

Strategies of avoidance

A post hoc re-analysis (**chapter 3**) suggests that the conclusions by Gøtzsche and Johansen [10] are valid for the strategy of concurrent bedroom interventions (an approach using combined a priori defined barriers for the treatment of the bedroom) as defined by Colloff [12]. This strategy was primarily executed in a minimalistic manner. The rarely tested strategy of air purification [13] exhibited potential in terms of the effect size; a medium reduction in the standardized mean difference (SMD) of the outcomes of the asthma symptom score (SMD = -0.53; n = 70) and a marginal reduction in medication usage

(SMD = -0.17; n = 72) were observed. Both reductions were not significant (respectively P = 0.19 and P = 0.46), which could also be explained by the limited sample sizes. This potential was extended by the significant results we observed in an updated meta-analysis on air purification for the treatment of domestic environment-related allergic asthma.

The strategy of concurrent bedroom interventions

The strategy of concurrent bedroom interventions comprises three primary bedroom barriers, including mite-impermeable covers (barrier 1), monthly hot laundering of the bedding (barrier 2), and removal of the bedroom carpet (barrier 3) [12]. A meta-regression of the strategy of concurrent bedroom interventions shows that greater the number of barriers introduced, more significant is the reduction in dust mite load when the load was high at baseline (P = 0.02) (**chapter 4**). One of the recommendations from this field is to reduce at least 90% of the house dust mite load to achieve clinical effectiveness [12]. We observed that the house dust mite load from the mattress was reduced by approximately 90% on combining at least three barriers in the bedroom (figure 2).

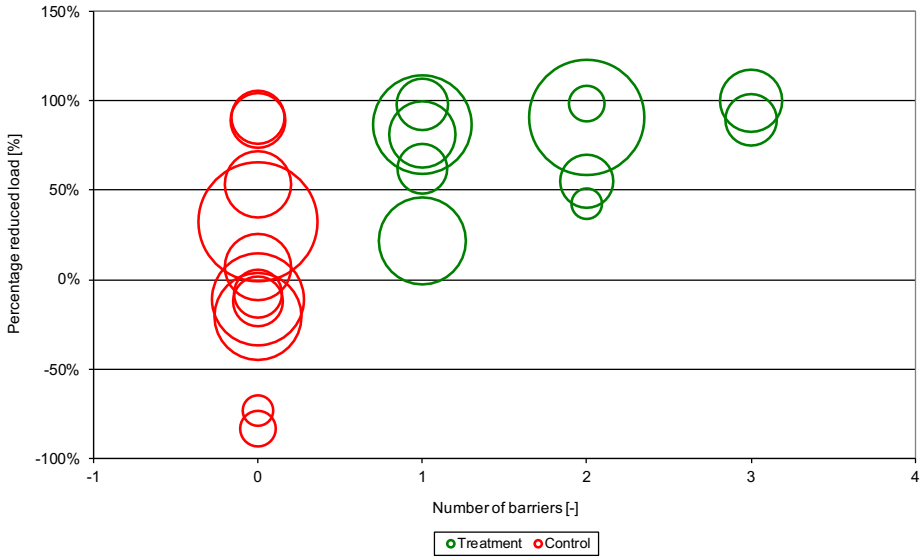

Figure 2. Scatterplot of percentage reduced mite allergen load from the mattress versus the number of barriers used in the strategy of concurrent bedroom interventions

The strategy of air purification

To investigate the potential of the air purification strategy, we updated the meta-analysis by McDonald et al. [13] by reviewing the effectiveness of HEPA filters for the treatment

of home-related allergic asthma (dust mite, dog, cat, and cockroach allergens) (**chapter 5**). Similar to the trend observed in the baseline characteristics, several trials on air purification for the treatment of home-related allergic asthma studied patients with predominantly mild to moderate asthma outcomes, resulting in marginal improvements, with varying significance. We observed statistically significant mean differences in the Asthma Quality of Life (AQLQ) scores (MD = +0.36; P = 0.01; n = 302) and the Fractional exhaled nitric oxide (FeNO) levels (MD = -6.67 ppb; P = 0.0008; n = 304). The SMDs in the asthma symptom scores reduced not significant (SMD = -0.68, P = 0.20), the medication usage (SMD = 0.01, P=0.94), the forced expiratory volume in 1 second (FEV_1 %pred.) (SMD = -0.11, P=0.34), and the PC_{20} (SMD = + 0.24, P = 0.53) were not significant. The two trials [14,15] responsible for the significant improvements were both sponsored by Airsonett AB, Angelholm, Sweden. For both trials, the possibility that the use of medication modified the results cannot be excluded, necessitating independent and more rigorous replication studies. A pertinent question is whether the effectiveness of intervention would become significant in patients with more severe and/or uncontrolled asthma. In the data on air purification, this issue is recognized in the outcomes of AQLQ and FeNO. In both outcomes we observed marginal yet statistically significant improvements (MD = +0.36 in AQLQ; MD = -6.67 ppb in FeNO). Notably, the trial by Boyle [15] on the use of a nocturnal laminar airflow reported that in the data limited to patients classified as requiring GINA step 4 therapies with poor control (ACT < 18), the mean difference in AQLQ (+0.70; P = 0.02; n = 87) and FeNO (-29.7 ppb; P = 0.001; n = 87) became clinically and statistically significant. Another pertinent question is whether combining the air purification strategy with a textile-based strategy would improve the clinical effectiveness, as results indicate that the use of high-efficiency particulate air (HEPA) filters does not eliminate allergen emissions [16].

House dust mites and altitude

The abundance of house dust mites varies in various regions of Europe [17]. Dry winter climates are known to limit house dust mite populations [18]. This is supported by the observations of house dust mite allergen exposure in the Scandinavian countries and the European Alps [19]. At a high altitude, other environmental factors, such as the barometric pressure and oxygen content, change as well [20]. In a hypotheses-generating meta-analysis, we studied whether altitudinal characteristics concurrently affect the survival of house dust mite populations (**chapter 6**). We observed several associations between house dust mite allergen exposure and multiple altitudinal characteristics, including the barometric pressure and oxygen content. When limiting the sampling locations to areas around the European Alps, the house dust mite allergen exposure was only associated with the oxygen content, while it did not correlate to the outdoor temperature in January as a substitute for the indoor humidity. The results necessitate

an experimental validation of house dust mite survival at a high altitude when exposed to optimal climatic conditions. If the development of house dust mites would (additionally) be associated with the oxygen content, this could create the possibility for a new environmental limiting strategy. In that case, it could be explored whether temporarily limiting the oxygen content in domestic textiles controls the survival of house dust mite populations.

Describing fluctuating house dust mite aeroallergen measurements

The paradigm of house dust mite allergen exposure relates to the bedding site [2]. Two recent pilots on the measurement of house dust mite aeroallergen exposure revealed exposure patterns varying with time [8, 9]. These pilots suggested that beds are not always the primary sites of exposure. Measurement of personal aeroallergen exposure is a relatively new concept [7]. We observed that the measurements of house dust mite aeroallergen exposure are commonly summarized using the mean (**chapter 7**). Furthermore, in a pilot on dust emission from the bedding site, we observed that the peak values differed substantially from the mean values (2:4 ratio), necessitating the measurement of daily house dust mite aeroallergen exposure using methods such as time series analysis. It remains to be addressed whether the use of more sophisticated mathematical models would alter the recent conclusions by Tovey et al. [9]. The study describing house dust mite aeroallergen exposure is based on the hypothesis that peak values are of relevance in the management of allergic asthma. This hypothesis is yet to be evaluated. In our meta-analysis of the strategy of air purification, significant improvements in AQLQ and the FeNO were observed using the Protexo (Airsonett, Angelholm, Sweden), contrary to the ASS and FEV_1 outcomes [15]. In another environmental study, Gore et al. [16] observed that the Protexo preliminarily reduced the decay and the background levels of aeroallergen exposure, and not their peak levels. This reflects the relevance of peak exposure in the direct immune reaction.

GENERAL CONSIDERATIONS

Restarting the debate?

As mentioned earlier (see page 16), the debate on house dust mite allergen avoidance reached an impasse since only comments were added to the meta-analysis by Gøtzsche and Johansen [10]. No new data backed by the same level of evidence have been added. Our meta-analyses are backed by the same level of evidence, highlighting the limitations in the study by Gøtzsche and Johansen [10] in particular. The potential for possible novel insights restarting the debate follows from the discrepancies in the study that were not addressed to date. Studying the patients with severe and uncontrolled asthma, indoor

environments with a high degree of allergen exposure, and the use of appropriate strategies of avoidance would help ascertain whether the existing information will be altered. These discrepancies should be studied in a concurrent manner. We were not able to test these hypotheses simultaneously due to the absence of clinical trials meeting the eligibility criteria of these end-points, particularly trials studying textile-based strategies. In fact, we urge the design of new clinical trials on the effectiveness of environmental control in allergic asthma treatment. The next sections discuss elements of the discrepancies we observed.

Studying the patients with severe asthma: the epidemiologic evidence

An aspect that is not discussed extensively is the threshold level of house dust mite allergen exposure for development of asthmatic symptoms in sensitised patients. Early epidemiological studies defined a threshold level of 10 μg mite allergen per gram of dust, above which asthmatic patients with house dust mite allergy would be in risk of an asthma exacerbation [2]. Studies linking the house dust mite allergen load to the severity of asthma outcomes are rare. In a study of 53 asthmatic adults, Custovic et al. [21] reported a moderate correlation (R^2 = 0.35 to 0.49) between several allergic asthma outcomes (PC_{20}, peakflow, and FEV_1 %pred.) and the exposure levels. This indicates that the threshold for symptom development differs for each patient, and a higher exposure corresponds to a greater number of patients at risk of displaying symptoms. In the study by Custovic et al. [21], a very low FEV_1 %pred. (<50%) was reported in a patient exposed to considerably low levels of allergens (>1 μg Der p2/g dust). Considering these factors concurrently, we surmise that questions pertaining to the threshold level require additional insights.

Investigating houses with a high degree of allergen exposure

A relevant issue for future studies is to identify indoor environments with a sufficient degree of allergen exposure. This question is related to the expected humidity of the niches where house dust mites are detected. House dust mites require a high relative humidity to survive [22]. A few technical aspects can be considered with respect to this issue. In the Netherlands, the current building regulation requires the development of well-insulated housing facilities [23]. The thermal insulation results in a lower relative humidity in carpets due to an increased temperature [24], imposing greater restrictions on house dust mite reproduction. This tendency is confirmed by findings on exposure in energy-efficient buildings in Lausanne [25]. Conversely, environmental research indicates that the microclimate in the bedding is also affected by the generation of heat and moisture from humans [26]. Apart from this, four human factors influence the microclimate in carpets and beddings [27]: the use of a heating system, the arrangement of furniture in houses; the human-mediated increase in humidity, and the use of a

building ventilation system. Therefore, the microclimate in the niche is determined by technical factors such as thermal insulation and presence of building ventilation, as well as by human factors [27]. Finally, the climatic change will create a more humid outdoor climate worldwide, improving the indoor climatic conditions for house dust mite survival [28]. Therefore, identifying indoor environments with a high degree of allergen exposure in the Netherlands would become easier. Nevertheless, in an older and extensive Dutch epidemiological study on the effectiveness of mite-impermeable covers for preventing mite allergy, the mean house dust mite allergen load from the mattress ranged from 0.6 to 5.1 μg/g dust during a period of eleven years [29]. This study presents the challenge of investigating patients exposed to high concentrations (>10 μg/g dust; [2]) of house dust mite allergens in the Netherlands. In countries with a warm and humid outdoor climate, such as in southern Europe or in the tropics, one will often detect higher levels of exposure [17].

Revisiting the exposure-based strategy?

Our meta-analyses were limited to results from peer-reviewed randomized blinded trials. The Cochrane methods recommend considering the inclusion of unpublished studies in systematic reviews [30]. Including data from unpublished trials reduces the risk of reporting bias. The only randomized blinded trial known to us from non peer-reviewed sources was conducted by Van Lynden- van Nes [31]. This thesis described the treatment of asthmatic children using the exposure-based strategy. While Kniest et al. [32] and Kort et al. [33] observed benefits using the same approach for the treatment of rhinitis and eczema, Van Lynden- van Nes [31] did not observe benefits in asthma treatment. Notably, Van Lynden- van Nes [31] also observed that 80% of the treatment group did not complete the exposure-based avoidance process. The latter is possibly the most relevant observation from this trial. It indicates that the evaluation of the exposure-based control necessitates an adaptive experimental design [34].

Notes on the policy of avoidance

The policy of avoidance is another issue of interest. In the general introduction, we introduced the concept of environmental neutrality (see page 15). This policy aims to bring the current exposure to a complete standstill. To the best of our knowledge, the application of this policy is yet to be studied. In the absence of environmental control (as recommended by Gøtzsche and Johansen [10]) this policy could hypothetically be relevant to patients' practice. Custovic et al. [21] showed that the severity and clinical activity of allergic asthma is positively related to house dust mite exposure. Van der Pol et al. [35] showed that in patients with house dust mite-induced allergic asthma who were already exposed in their personal environment, a bronchial allergen challenge with house dust mite allergen resulted in increased immune responses. In other words, the

allergen challenge investigated by Van der Pol et al. [35] should be considered to correspond to an increase in personal exposure, which subsequently resulted in an increase in immunologic parameters. Its implication on patient practice remains unclear. In absence of environmental control of the house dust mite allergens, the allergen exposure is still expected to undergo a yearly rise based on ecological principles [36]. House dust mite populations will increase until the mites reach an optimal density [36]. This process of population development can take several years. Concurrently, the faecal products of house dust mites remain allergenic for several years [37]. Taken together, the immune response and related symptoms can hypothetically still worsen in long-term when control of allergen exposure is not practiced. Application of this hypothesis can be considered in the guideline by the American Academy of Allergy, Asthma, and Immunology, recommending positive on measures for avoidance [38]. To the best of our knowledge, this hypothesis has not yet been studied in a controlled setting.

Other discrepancies possibly playing a role

Finally, our meta-analyses were based on randomized trials conducted from 1976 [39] to 2017 [40]. In several outcomes, we observed unknown variability between the studies. A priori defined covariates such as house dust mite allergen exposure, adult versus child and/or co-sensitization did not explain the variability in the subgroups that we were able to investigate. Other possible relevant covariates could be the several medical issues that changed during the last decades, which also relate to the changes in the effectiveness of house dust mite allergen avoidance for the treatment of asthma. For instance, the guidelines introduced new pharmacological strategies for asthma management, such as the recent recommendation by GINA for treating adult patients using a symptom-driven method [in mild asthma] or a daily corticosteroid-containing inhaler [41]. As a result, the medication use at baseline altered in the period we studied. Another issue is that standardized questionnaires were introduced for measuring asthma control as well as the quality of life [42, 43]. Possibly, the non-standardized questionnaires were responsible for introducing variance. Additionally, changes in the measurement of the allergen concentration could play a role [7]. To investigate these possible explanatory variables, the results should be sub-grouped based on a specific period.

CONCLUSIONS AND RECOMMENDATIONS

The current evidence on the absence of benefits of treating house dust mite-induced allergic asthma using environmental means is characterised by limitations in patient selection, their indoor environment, and is valid for the strategy of concurrent bedroom interventions. The discrepancies in existing research can be addressed by investigating

patients with more severe and uncontrolled asthmatic conditions, and adopting comprehensive environmental strategies for treating patients exposed to high house dust mite levels at baseline. Framing relevant future research questions for such non-studied subgroups might help us reverse the impasse in this debate. Apparently, the description of exposure in trials can be improved by measuring the airborne concentration of house dust mite allergens, and describing the peak as well as the mean exposures. We observed the potential of the strategy wherein air purification improves the AQLQ scores and FeNO levels of patients with home-related allergic asthma with the use of a nocturnal laminar airflow. Possibly, other environmental factors, such as oxygen content, offer new avenues for exploring controlling strategies.

It has been recommended previously that randomized trials on house dust mite avoidance should be methodologically rigorous [10]. Several factors influence the exposure to house dust mite allergens. The control of all these factors in a trial is complicated. Therefore, the design of adaptive trials should be considered. In addition to the recommendations by Gøtzsche and Johansen [10], we recommend future randomized controlled trials on environmental means to investigate the discrepancies presented above. Strategies of house dust mite allergen avoidance, including exposure-based control, should be tested; the strategy of concurrent bedroom interventions should be executed with at least four barriers, and a purified nocturnal laminar airflow combined with a textile-based approach should be employed.

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CHAPTER 9

Summary

Samenvatting

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SUMMARY

Asthma is a heterogeneous disorder of the conducting airways. One of the factors responsible for the onset of allergic asthma is exposure to indoor aeroallergens, particularly to the allergen from house dust mites. Allergic asthma can be treated using pharmacotherapy, immunotherapy, and by avoidance of allergen exposure. At the highest level of evidence, no clinical benefits of avoiding indoor aeroallergen exposure were observed. The debate on the effectiveness of environmental control for the treatment of house dust mite allergic asthma reached an impasse.

In this thesis, we investigate several aspects of the predominant Cochrane review on house dust mite allergen avoidance that have not been studied yet (Cochrane Database of Systematic Reviews, 2008, Art. No: CD001187). First, we describe a meta-analysis of the baseline characteristics in the trials evaluated by Gøtzsche and Johansen (**chapter 2**). In 45 trials, we could denote the house dust mite allergen load from the mattress (mean 9.86 µg/g dust, 95% CI: 5.66 to 14.05 µg/g dust), the standardized asthma symptom scores (mean 0.13, 95% CI: 0.08 to 0.18), the forced expiratory volume in one second (FEV_1) % predicted (mean 85.3%, 95% CI: 80.5 to 90.1%), and the histamine or methacholine concentration that causes a 20% reduction in the FEV_1 at baseline (mean PC_{20} 1.69 mg/mL, 95% CI: 0.86 to 2.52 mg/mL). The outcomes indicate that several clinical trials investigated patients with rather mild to moderate allergic asthma who were exposed to varying and sometimes negligible levels of allergen. In more than half of the included trials (56%), patients used inhaled corticosteroids, possibly explaining the predominantly moderate asthma status at baseline.

Strategies of house dust mite allergen control have been defined before (**chapter 3**). Total avoidance and a sojourn to a house dust mite-free environment were methods adopted initially. In the nineties, two textile-based approaches were introduced: the exposure-based strategy and the concurrent bedroom interventions. Other strategies include the breathing-related and combined strategies. We executed a post hoc subgrouping of the results into categories based on the environmental strategy used for house dust mite allergen control, revealing that the current evidence primarily relates to the strategy of concurrent bedroom interventions, executed in a minimalistic manner. The rarely investigated strategy of air purification exhibits potential based on a non-significant improvement of the asthma symptom scores (SMD = -0.53) and medication usage (SMD = -0.17) in a small sample size.

Concurrent bedroom intervention is the strategy predominantly evaluated in clinical trials (**chapter 4**). This strategy comprises three primary bedroom barriers (interventions), including a mite-impermeable cover (barrier 1), monthly hot laundering (temperature≥60 °C) of the bed sheets (barrier 2), and removal of the bedroom carpet and soft toys (barrier 3). An investigation of this strategy revealed that a majority of the clinical trials studied the effectiveness of a minimalistic execution of concurrent bedroom interventions (one

or two barriers). Only two small trials introduced the three barrier concept. Our post hoc re-analysis suggests that a greater number of barriers corresponded to a more significant reduction in dust mite allergen load when the load was high at baseline (P = 0.02). The number of trials were considerably limited to allow an appropriate examination of health outcomes related to the execution of the concurrent bedroom strategy.

A strategy with significant clinical potential is the purification of indoor air (**chapter 5**). We updated the existing meta-analysis on the effectiveness of the air purification strategy for the treatment of home-related allergic asthma. In two trials, we observed marginal yet significant improvements in the outcomes of the Asthma Quality of Life Questionnaire (AQLQ) score (MD = +0.36) and the fractional exhaled nitric oxygen (FeNO) levels (MD = -6.67 ppb) with the use of a nocturnal laminar filtered airflow. No effectiveness was observed in the standardized mean differences in the asthma symptoms scores (SMD = -0.68), the use of medication (SMD = 0.01), the FEV_1 % predicted (SMD = -0.11), and the bronchial hyperresponsiveness PC_{20} (SMD = + 0.24).

The abundance of house dust mites in Europe is associated with the mean outdoor temperature in January (P = 0.0006), which is a substitute for the indoor humidity during the winter season (**chapter 6**). When sampling locations were limited to areas around the European Alps, house dust mite survival was only associated with the oxygen content (P = 0.02). This suggests the possibility that oxygen content is an environmental factor limiting house dust mite survival.

The last study dealt with the issue of describing airborne allergen exposure measurement (**chapter 7**). Reports on the measurement of house dust mite aeroallergens reveal that these measurements are commonly summarized using the mean value. From the results of a pilot on dust emissions after shaking a duvet, we observed that peak concentrations differed substantially from mean concentrations (2:4 ratio). The statistical description of house dust mite aeroallergen exposure released from bedding materials necessitate the use of sophisticated mathematical models, such as a time series analysis.

On the basis of our meta-analyses, we conclude that the current evidence on the absence of benefits of the treatment of house dust mite-induced allergic asthma using environmental means is characterised by limitations in the selection of the patients, their indoor environment, and the type of intervention evaluated. The discrepancies include the consideration of patients with more severe conditions who were also exposed to high allergen concentrations, and the testing of comprehensive control strategies. The fourth meta-analysis indicates the potential of the air purification strategy marked by the improvement of the AQLQ scores and the FeNO levels in patients with home-related allergic asthma. An observational meta-analysis on altitudinal characteristics suggests new opportunities for exploring oxygen content as a limiting factor for house dust mite survival. Based on the sixth study, we recommend that future studies should describe the house dust mite aeroallergen exposure using both peak and mean values.

SAMENVATTING

Astma is een ziekte van de onderste luchtwegen die veel variatie kan vertonen. Blootstelling aan binnenhuisallergenen, in het bijzonder die van de huisstofmijt, is een belangrijke oorzaak van de ontwikkeling van allergisch astma. Allergisch astma kan worden behandeld met medicatie, immunotherapie en het vermijden van blootstelling aan allergenen. Op het hoogste niveau van bewijs konden echter geen klinische verbeteringen worden aangetoond voor het vermijden van binnenhuisallergenen ter behandeling van astma. Het debat over de effectiviteit van vermijden van huisstofmijt allergenen voor de behandeling van allergisch astma kwam in een impasse terecht.

Dit proefschrift bestudeert meerdere nieuwe aspecten van de overheersende Cochrane review van Gøtzsche en Johansen naar het vermijden van huisstofmijt allergenen (Cochrane Database of Systematic Reviews, 2008, Art. No: CD001187). Eerst evalueren we de beginwaarden uit de trials die Gøtzsche en Johansen bestudeerden, door middel van een meta-analyse (**hoofdstuk 2**). In vijfenveertig trials vonden wij de allergeen expositie van de matras beschreven (gemiddeld 9.86 µg/g stof, 95% BI: 5.66 tot 14.05 µg/g stof), een gestandaardiseerd astma symptoom score (gemiddeld 0.13, 95% BI: 0.08 tot 0.18), een "forced expiratory volume in 1 second (FEV_1)" (het uitgeblazen luchtvolume tijdens de eerste seconde van de test) in voorspeld percentage (gemiddeld 85.3%, 95% BI: 80.5 tot 90.1%), en de histamine- of metacholine concentratie waarbij het FEV_1 20 procent daalt (gemiddelde PC_{20} 1.69 mg/mL, 95% BI: 0.86 tot 2.52 mg/ml). Deze uitkomsten suggereren dat in veel klinische trials patiënten met vrij mild tot matig astma zijn bestudeerd, die waren blootgesteld aan wisselende en soms verwaarloosbare niveaus van binnenhuis allergenen. De matige astma status bij aanvang van de studies wordt waarschijnlijk verklaard door het gebruik van corticosteroïden, wat in meer dan de helft van de studies (56%) speelde.

In de loop der jaren zijn diverse strategieën ter vermijding van huisstofmijt allergenen gedefinieerd (**hoofdstuk 3**). Totale vermijding en verblijf in een mijtvrije omgeving werden als eerste geïntroduceerd. In de negentiger jaren volgden twee textielgebaseerde aanpakken; de "expositie gebaseerde strategie" en de "samengestelde slaapkamermaatregelen". Andere strategieën richten zich op de binnenlucht, als ook het mixen van strategieën. Een post hoc- categorisering van de resultaten van Gøtzsche en Johansen naar strategieën toont dat de samengestelde slaapkamerinterventies verreweg het meest zijn bestudeerd, daarbij vaak op een minimale wijze uitgevoerd. De schaars beproefde strategie van luchtzuivering toonde potentie via een niet-significante verbetering in het astma symptoom score (SMD = -0.53) en het gebruik van medicatie (SMD = -0.17) in een kleine steekproef.

De klinische trials naar vermijding van blootstelling aan allergenen worden gedomineerd door het testen van de strategie van de samengestelde slaapkamer interventies (**hoofdstuk 4**). Deze strategie is opgebouwd uit drie primaire interventies in de slaapkamer, te weten het toepassen van allergeenvrije hoezen (barrière 1); het maandelijks heet wassen (temperatuur ≥ 60 ºC) van alle lakens (barrière 2); en het verwijderen van overige textiel uit de slaapkamer (tapijt en knuffeldieren) (barrière 3). Uit een verkenning naar deze strategie blijkt dat de meeste trials een minimale uitvoering van de samengestelde slaapkamerinterventies hebben bestudeerd (één of twee barrières). Twee kleine trials bestudeerden een interventie bestaande uit drie barrières. Een post hoc heranalyse van de resultaten van Gøtzsche en Johansen geeft aan dat des te meer barrières worden geïntroduceerd, des te meer allergeen expositie wordt gereduceerd als deze bij aanvang van de studie hoog is (P = 0.02). Het aantal beschikbare trials was in deze heranalyse te klein om de klinische effectiviteit te kunnen beoordelen.

Een strategie die klinische potentie vertoond is luchtzuivering (**hoofdstuk 5**). Een oudere meta-analyse (2002) naar de effectiviteit van luchtzuivering binnenshuis ter behandeling van allergisch astma is bijgewerkt. In twee trials naar luchtzuivering direct boven het bed verbeterde de uitkomsten kwaliteit van leven bij astma (MD = +0.36) en de fractie uitgeademde stikstofoxide (MD = -6.67 ppb) beperkt doch significant. Geen significant verschil werd gevonden voor de gestandaardiseerde astma symptoom score (SMD = -0.68), het gebruik van medicatie (SMD = 0.01); het voorspelde percentage FEV_1 (SMD = -0.11); en de bronchiale hyperreactiviteit PC_{20} (SMD = +0.24).

De verdeling van huisstofmijten over Europa is gerelateerd aan de gemiddelde buitenluchttemperatuur in januari (P = 0.0006), als maat voor de binnenluchtvochtigheid in het winterseizoen (**hoofdstuk 6**). Als de data van huisstofmijtenexpositie over Europa worden beperkt tot een gebied direct rondom de Alpen, blijft alleen nog een associatie tussen de expositie en het zuurstofgehalte van de lucht over (P = 0.02). Dit suggereert dat het zuurstofgehalte van de lucht ook een beperkende factor zou kunnen zijn voor huisstofmijtpopulaties.

Het laatste hoofdstuk is gewijd aan het beschrijven van meetgegevens van aerosole allergeenexpositie (**hoofdstuk 7**). Publicaties over metingen naar aerosole huisstofmijt allergenen beschrijven deze in het algemeen met het gemiddelde. In een pilot naar stof emissie uit geschud beddengoed blijkt dat piekexposities veel verschillen van de gemiddelde blootstelling (verhouding 2 tot 4). Het beschrijven van aerosole huisstofmijt allergenen vraagt om het gebruik van maatwerk statistieken, zoals een tijdreeks analyse.

Op basis van onze meta-analyses concluderen wij dat het huidige gebrek aan bewijs voor klinische effectiviteit van vermijding aan blootstelling voor de behandeling van astma wordt gekenmerkt door beperkingen. Minder of niet bestudeerd zijn patiënten met ernstig en ongecontroleerde astma, blootgesteld aan een hoge allergeen expositie. Qua

strategie dienen uitgebreide interventies te worden getest. De vierde meta-analyse laat potentie zien voor de strategie van luchtzuivering middels verbeteringen in de kwaliteit van leven en de fractie uitgeademde stikstofoxide. Een meta-analyse naar hooggebergte karakteristieken en huisstofmijtenexpositie suggereert nieuwe kansen voor onderzoek naar het zuurstofgehalte als beperkende factor voor de huisstofmijt. Uit de laatste studie volgt het advies om in volgende studies de aerosole huisstofmijtallergenen zowel met piekwaarden als het gemiddelde te beschrijven.

ABOUT THE AUTHOR

Frank van Boven was born on August 11, 1968 in The Noordoostpolder, The Netherlands. He grew up in Ede and attended the Middelbare Technische School Ede (Technical Secondary School). In 1987 he started his Bachelors study at the Hogeschool of Utrecht's Building Technology Department. Subsequently, he specialised in the field of building physics. After graduating with distinction in 1991, he continued studying Building and Architecture at the Eindhoven University of Technology. In Eindhoven, he specialised in the field of biotic agents in the built environment, attending elective lectures on mathematical statistics at the Department of Mathematics. In 1994, he received his Master of Science Degree in Building and Architecture upon completing a final project on building measures against cockroaches. In 1995 he attended a one-year post graduate course on environmental noise control at the Hogeschool Amsterdam.

After graduating, Frank was employed for several years in the industry of building products in both building physic and consulting engineering. He worked as a policy maker for safety management for the city of Capelle aan den IJssel, as of December 1999. During the period 2000 through 2006, Frank taught Dutch respiratory care-nurses the basics of building physics for the Dutch Stichting Specifieke Scholing Verpleegkundigen (SSSV) in Bunnik.

The period at SSSV laid the foundation for the current research on house dust mite allergen avoidance. From 2007 to 2008 Frank was a visiting researcher at the chair of Public Health Engineering for Built Environments (PHEBE) of Eindhoven University of Technology. At PHEBE, he studied the relationship between dust mites and indoor environment, and guided students. A visit to the Congress of the European Academy of Allergy and Clinical Immunology of 2009, Warsaw, attracted his attention to the debate on the clinical effectiveness of house dust mite allergen avoidance. He now is a researcher at the Section of Allergology and Clinical Immunology, Department of Internal Medicine, Erasmus Medical Center Rotterdam. At the Section of Allergology and Clinical Immunology, he studies interdisciplinary issues in the debate on the clinical effectiveness of allergen avoidance.

In 2004 he married Leilani Ruma and in 2006 their son Rodney was born.

PORTFOLIO

Publications

Peer-reviewed publications

- Boven van, F. E., De Jong, N.W., Braunstahl, G. J., Arends, L.R. & Gerth van Wijk, R., (2020), Effectiveness of the air purification strategy for the treatment of allergic asthma: a meta-analysis, International Archives of Allergy and Immunology 2020, DOI: 10.1159/000506284
- Boven van, F. E., De Jong, N.W., Braunstahl, G. J., Gerth van Wijk, R., & Arends, L. R. (2020), A meta-analysis of baseline characteristics in trials on mite allergen avoidance in asthmatics: room for improvement, Clinical and Translational Allergy, 10:2, 1-12
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- Boven van, F.E. (2014), Effectiveness of mite-impermeable covers: a hypothesis generating meta-analysis, Clinical & Experimental Allergy (44), 1473-1483

Book chapters

- Boven van, F.E. (2015), House dust mites and altitude, In: T. White (Ed.), Termites and Mites: Distribution Patterns, Biological Importance and Ecological Impacts (Nova Science Publishers)

Conference abstracts

- Boven van, F.E., De Jong N.W., Loomans M.G.L.C., Braunstahl G.J., Gerth van Wijk R., Arends L.R. (2020), Describing indoor house dust mite aeroallergen exposure: Inclusion of peak concentrations, European Aerosol Conference - EAC 2020 (abstract accepted)
- Boven van, F.E. (2013), Dose response for predicted FEV_1: a preliminary meta-analysis, European Congress of Epidemiology, Aarhus, Denmark (poster)
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- Boven van, F.E., J.E.M.H. van Bronswijk and S. Kuhnt (2010), Combined environmental characteristics affecting mite-allergen load (*Acari*) in a small sample from Dutch mattresses, 29th Congress of the European Academy of Allergy and Clinical Immunology, London, United Kingdom (oral presentation)
- Boven van, F.E. and G. Schober (2010), Is mite allergen exposure at high altitudes affected by multiple environmental characteristics?, 29th Congress of the European

Academy of Allergy and Clinical Immunology, London, United Kingdom (oral presentation)
- Boven van, F.E. (2010), Concepts of applying impermeable covers for control of asthma: a preliminary review, 29th Congress of the European Academy of Allergy and Clinical Immunology, London, United Kingdom (poster)
- Boven van, F.E. (2009), Reproducibility of questions on environment characteristics related to mite allergen load independent from education on environment, 28th Congress of the European Academy of Allergy and Clinical Immunology, Warsaw, Poland (poster presentation)
- Boven van, F.E. (2009), Assessing airborne exposure from beddings by means of environmental engineering, 28th Congress of the European Academy of Allergy and Clinical Immunology, Warsaw, Poland (poster)
- Boven, F.E. van, S. Kuhnt and J.E.M.H. van Bronswijk (2008), Combined analysis of environmental characteristics affecting mite allergen load (*Acari*) in Dutch bedrooms, Indoor Air, Copenhagen, Denmark (oral presentation)

Invited lectures
- Boven van, F.E. (2011), Closed or open doors? Avoidance of indoor allergen and pollutant exposure, Rotterdam (pre-congress of International Society for Aerosols in Medicine)

Education, courses and workshops

- July 2019, Research integrity, Erasmus Medical Center, Rotterdam (1 day course)
- February 2015, Ontwikkelen van een Cochrane Review over interventies, Cochrane Netherlands (2 days workshop)
- July - October 2014, Understanding Research: An Overview for Health Professionals, University of California, San Fransisco (online course, Coursera)
- March - May 2014, Academic writing English, Leiden University (5 days course)
- June 2013, workshop "The New Statistics" by Geoff Cumming, Utrecht University (1 day)
- January 2007 – November 2008, Publication class, Chair Public Health Engineering for Built Environments, Eindhoven University of Technology
- Sept. 1995 – Jun. 1996, Amsterdam University of Applied Sciences, Post-course environmental noise control
- Sept. 1991 - Aug. 1994, Eindhoven University of Technology; Faculty of Building and Architecture, building physics; Graduated in the field of biotic agents in the built environment (Elective lectures were attended in mathematical statistics)

- Aug. 1987 – Jul. 1991, Utrecht University of Applied Sciences; Faculty of Building Technology (graduated with distinction)

Teaching

- 1999 – currently, instructing of Dutch respiratory nurses in technical diagnoses of the indoor environment, and methods of allergen avoidance
  - Stichting Specifieke Scholing Verpleegkundigen, Bunnik (Applicatiecursus Saneren, 1999 to 2006)
  - V&VN Longverpleegkundigen, Utrecht (workshops 2011, 2013, 2014, 2016, 2019)
  - Antonius Academie, Utrecht (Course Asthma / COPD, as of 2017)
  - Davos Asthma on Top (2019)
- 2007 – 2008, Instruction of Bachelor and Master students, Chair of Public Health Engineering for Built Environments, Eindhoven University of Technology
  - 2007: Health and Comfort seven students
  - 2008: Robotics three students
  - 2008: Health and Comfort six students

Miscellaneous

Bachelor-students
Supervising internalships at Municipal of Capelle aan den IJssel including writing of the Bachelor-thesis: six students (2012 – 2017).

Memberships
July 2006 – currently, Member of the Dutch commission on allergen avoidance, V&VN Lung Care nurses, Utrecht (Acting Chairman as of November 2012)

DANKWOORD

Allergeenvermijding is een onderwerp dat mij al gedurende zeer lange tijd interesseert. Tijdens mijn studie Bouwfysica aan de Technische Universiteit Eindhoven van 1992 tot 1994 kon ik via de leerstoel van prof dr. Annelies van Bronswijk al kennis maken met onderzoek naar de huisstofmijtenallergie. Rond de millennium-wisseling startte ik met lesgeven in toegepaste bouwfysica aan longverpleegkundigen (1999-2006) bij de Stichting Specifieke Scholing Verpleegkundigen. Centraal stond de vraag hoe een bouwkundige een woning analyseert. Ideeën ontstonden over een gestandaardiseerd bouwkundig meetinstrument voor de longverpleegkundige en ook het vraagstuk van allergeenarm wonen. Daarna keerde ik voor een korte periode terug naar prof.dr. Annelies van Bronswijk en volgde deelname aan haar publicatieklas. Hiermee kwam er meer structuur in mijn onderzoek en het beschrijven van de bevindingen. Waar ik mij eerst nog richtte op de allergeenarme woning, werd ik in 2009 door het bijwonen van een lezing van prof. dr. Roy Gerth van Wijk over allergeenvermijding op het EAACI-congres met de neus op de feiten gedrukt. Er bleek geen evidence (meer) te zijn dat patiënten er baat bij hebben. Tijdens het lezen van het verantwoordelijke wetenschappelijke artikel van prof.dr. Gøtzsche en dr. Johansen (2008) viel ik al snel van de ene in de andere verbazing. Alle vormen van saneren werden ongeordend en in een eenvoudige analyse samengevoegd. Een nog belangrijker onderzoeksvraag openbaarde zich vervolgens dan het ontwerp van een allergeenarme woning, namelijk wat is het medische effect van saneren. Het belang van deze vraag werd bij iedere bijeenkomst van de werkgroep Saneren van de Verpleegkundigen & Verzorgenden Nederland onder leiding van Tiny Rooijendijk weer onderstreept en zorgde voor een belangrijke stimulans om door te blijven gaan. En nog steeds is het een belangrijk aandachtspunt in bijeenkomsten met de huidige leden Yvonne Verkooijen, Marieke Roest en Joke Hes. Dit alles leidde ertoe dat ik me ging verdiepen in het bewijs van effecten van allergeen vermijding op de klachten van de allergische patiënt. Met dank aan de nodige hulp van een groep mensen is het resultaat dit proefschrift.

Allereerst wil ik graag mijn promotor prof.dr. Roy Gerth van Wijk bedanken. Beste Roy, onze eerste ontmoeting dateert van rond 2009 toen wij het hadden over allergeenarm wonen. Nadat er een plan kwam voor het opnieuw bestuderen van de effectiviteit van allergeenvermijding, omarmde jij dit plan. Op natuurlijke wijze organiseerde jij een interdisciplinaire begeleiding, met ruimte voor iedere discipline voor zowel passende inbreng als samenwerking, waarvoor ik je graag wil bedanken. Ik wil je ook graag bedanken voor jouw strategische inbreng tijdens de onderzoeken, waardoor een artikel met een gewijzigde opzet kon worden gepubliceerd. Jouw begeleiding was altijd positief-kritisch, constructief en op samenwerking gericht. Bedankt voor het in mij gestelde vertrouwen.

Prof.dr. Lidia Arends, promotor. Beste Lidia, naast wetenschapper ben je ook heel sociaal, en jouw samenwerking met prof.dr. Roy Gerth van Wijk verliep dan ook van het begin prettig. Op subtiele wijze heb jij veel invloed gehad op mijn proefschrift. Niet alleen door het zetten van de punten op de "i" in mijn analyses, maar ook jouw sturing om het wiskundig eenvoudig en tegelijkertijd wetenschappelijk te houden verdient een vermelding. Wiskunde ligt mij na aan het hart. Anderzijds is het ook belangrijk om het werk geaccepteerd te krijgen onder clinici. Ook jouw begeleiding was altijd constructief en op samenwerking gericht. Graag wil ik ook jou bedanken voor het in mij gestelde vertrouwen.

Dr. Nicolette de Jong, co-promotor. Beste Nicolette, jij werd in een wat later stadium betrokken in het onderzoeksproject. Jouw rol lag naast inhoudelijke inbreng ook in het schenken van aandacht aan de wetenschappelijke mores rondom het schrijven van artikelen, die mij minder bekend zijn. Door jouw inbreng was het ook mogelijk de latere meta-analyses met dubbele data-extracties uit te voeren. Dat heeft de wetenschappelijke waarde flink verhoogd, en bijgedragen aan de acceptatie van de artikelen. Gaandeweg bleek dat wij elkaar versterken in het onderzoek. Waar ik graag wat afstand neem om alles nog eens te overdenken, geef jij juist gas bij. Dat was op het einde ook wel eens nodig. Ik wil je graag bedanken voor onze samenwerking en de energie die jij op het juiste moment hebt ingebracht!

Dr. Gert-Jan Braunstahl, co-promotor. Beste Gert-Jan, jij reageerde altijd snel op mijn concept-teksten. Belangrijk waren jouw adviezen om (kleine) bevindingen meer te etaleren. Wetende dat juist in het longdomein de afwezigheid van het bewijs van allergeenvermijding als interventie domineert, was jouw steun als longarts heel belangrijk om toch door te blijven gaan. Ik wil je graag bedanken voor misschien wel het belangrijkste aspect in het schrijven van de artikelen, meedenken en het oog blijven houden voor de klinisch gerichte lezer bij mijn "wat" technische schrijfstijl.

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Dr. Marcel Loomans, Technische Universiteit Eindhoven. Beste Marcel, graag wil ik jou bedanken voor het bewaken van de meer fysisch gerichte aspecten in het enige echte technische artikel. Aan het einde waren jouw tips van belangrijke waarde om het artikel op voldoende niveau te krijgen.

Anderen die ik graag wil bedanken voor hun bijdrage zijn Wichor Bramer (literatuuronderzoeken) en Wilma Bergen Henegouwen. Op de achtergrond kon ik altijd op Wilma rekenen als er faciliteiten nodig waren. Dr. Euan Tovey (The University of Sydney) en dr. Wolfgang Viechtbauer (Maastricht University) wil ik graag bedanken voor hun tips en hulp bij het uitwerken van hoofdstuk vier. Ravebo B.V. te Brielle maakte de metingen uit hoofdstuk zeven mogelijk.

Waar het hierna om gaat is dat er degelijk vervolgonderzoek van de grond komt, leidend tot betrouwbare uitkomsten en duidelijkheid voor de allergische patiënt. Ik hoop hiertoe met jullie allen in de toekomst nog meerdere artikelen te mogen schrijven.

Tot slot. Lieve Lanie en Rodney, de afgelopen jaren kostte het schrijven van dit proefschrift soms veel privé-tijd. Dank voor jullie steun en begrip! En Lanie ook nog voor haar accurate hulp bij de data-extracties!

APPENDICES

ANNEX TO CHAPTER 2

Reference search; keywords for embase.com

('Pyroglyphidae'/exp OR 'mite'/de OR 'Acari'/de OR 'house dust'/de OR 'house dust allergen'/de OR 'mite infestation'/de OR 'house dust allergy'/de OR 'dust exposure'/de OR (Dermatophagoid* OR mite OR mites OR 'D farinae' OR 'd pteronyssinus' OR Pyroglyphid* OR Euroglyph* OR 'e maynei' OR Acari* OR housedust* OR (dust NEAR/6 (allerg* OR sensiti* OR hypersensiti* OR indoor* OR house* OR domestic* OR asthma* OR ambient*))):ab,ti) AND ('air conditioning'/de OR 'exposure'/de OR 'dust exposure'/de OR 'environmental exposure'/de OR 'environmental parameters'/de OR 'avoidance behavior'/de OR 'environmental factor'/de OR 'environmental management'/de OR 'textile'/de OR 'home environment'/de OR 'tertiary prevention'/de OR 'microclimate'/de OR 'room ventilation'/de OR 'air quality'/de OR 'ambient air'/de OR 'air quality control'/de OR humidity/de OR 'environmental sanitation'/de OR 'sanitation'/de OR (avoidance* OR (impermeab* NEAR/3 cover*) OR ((humid* OR allergen* OR climate*) NEAR/3 (control* OR reduction*)) OR (air NEAR/3 (condition* OR filt* OR qualit* OR ambient* OR control* OR clean*)) OR ventilat* OR expos* OR textile* OR load OR environment* OR (dust NEAR/3 level*) OR anti-mite OR spray* OR mattress* OR management* OR (tertiary NEAR/3 prevent*) OR microclimate* OR micro-climate* OR sanitation OR bed-cloth* OR bed-cover* OR bedding OR furnish*):ab,ti) AND ('Controlled clinical trial'/exp OR 'Crossover procedure'/de OR 'Double-blind procedure'/de OR 'Single-blind procedure'/de OR (random* OR factorial* OR crossover* OR (cross NEXT/1 over*) OR placebo* OR ((doubl* OR singl*) NEXT/1 blind*) OR assign* OR allocat* OR volunteer* OR trial OR groups):ab,ti) NOT ([animals]/lim NOT [humans]/lim) NOT ([Conference Abstract]/lim) AND [English]/lim

List of included and excluded studies in the updated search

	Author	Year	Included?	Rationale
1	Eick	2011	No	not patients with house dust mite-allergic asthma
2	Glasgow	2011	No	excluded by Gotzsche and Johansen
3	Maas	2011	No	not tertiary prevention
4	Neymayr	2011	No	not a clinical trial
5	Takaro	2011	No	not randomized
6	Breysse	2012	No	not a clinical trial
7	Celano	2012	No	not patients with house dust mite-allergic asthma
8	El-Ghitany	2012	Yes	
9	Gehring	2012	No	not tertiary prevention
10	Ho	2012	No	abstract
11	Masna	2012	No	abstract
12	Scott	2012	No	not tertiary prevention
13	NCT	2013	No	protocol issue
14	Tsurikisawa	2013	No	not blinded
15	Hogaard	2014	No	abstract
16	NCT	2014	No	duplicate
17	Hogaard	2014	No	duplicate
18	Murray	2015	No	duplicate
19	Smith	2015	No	not blinded
20	Sumner	2015	No	duplicate
21	Dimango	2016	No	not patients with house dust mite-allergic asthma
22	NCT	2016	No	protocol issue
23	Tsurikisawa	2016	No	not blinded
24	Winn	2016	No	not a clinical trial
25	Luo	2017	No	abstract
26	Murray	2017	Yes	
27	Morten	2018	No	not patients with house dust mite-allergic asthma
28	Bjermer	2019	No	not a clinical trial

Number of trials available per subgroup

Category	FEV_1 %pred.	PC_{20}	Std. ASSs
Steroids	9	9	7
No steroids	5	5	4
Child	5	6	5
Adult	11	9	7
Co-sensitization	8	9	7
No co-sensitization	2	2	2

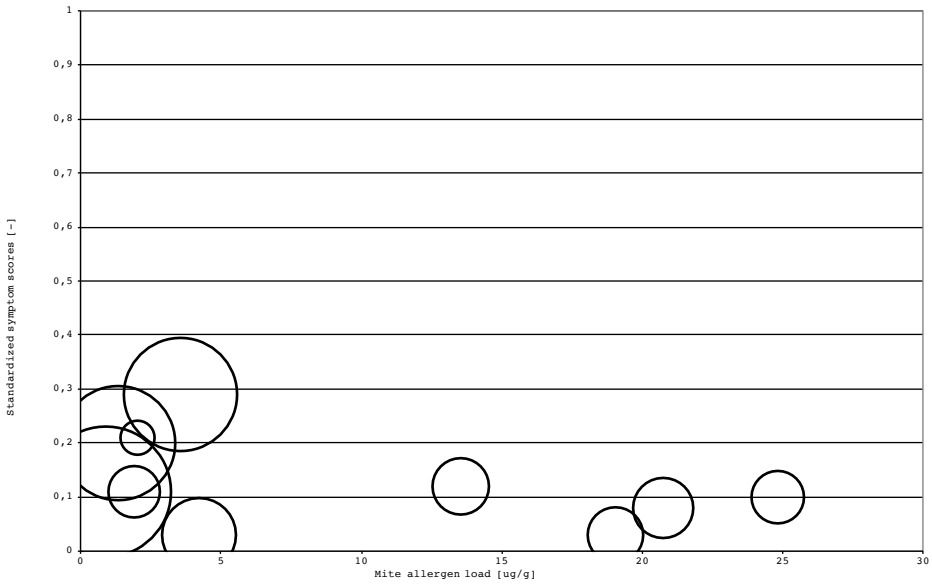

Figure A1. Scatterplot for the PC_{20} against the mite allergen load from the mattress at baseline.

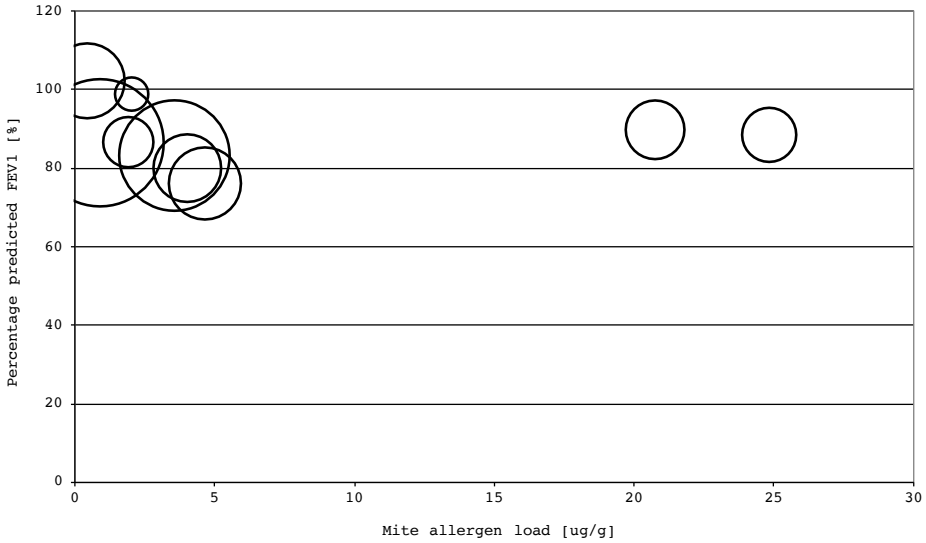

Figure A2. Scatterplot for the standardized asthma symptom scores against the mite allergen load from the mattress

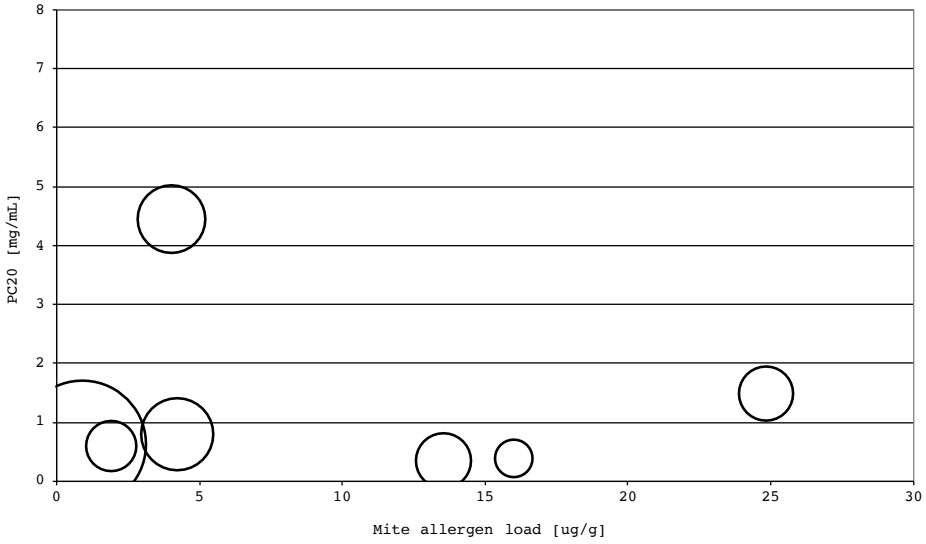

Figure A3. Scatterplot for the FEV_1 percentage of predicted against the mite allergen load from the mattress at baseline.

ANNEX TO CHAPTER 5

Table. Excluded twenty-nine full-text studies for not meeting our inclusion criteria.

First author	Year	Rationale for exclusion
Villaveces	1977	Incomplete data.
Kooistra	1978	Treatment of rhinitis.
Reisman	1990	Treatment of rhinitis (n = 21) or asthma (n = 11).
Warner	2000	Not the strategy of air purification.
Htut	2001	Not the use of a HEPA filter.
Francis	2003	Not blinded.
Swartz	2004	Not a RCT.
Eggleston	2005	Control received the intervention at the end of the study.
Nct	2005	Not a RCT.
Nct	2005	Not a RCT.
Thomson	2005	Not a RCT.
Wright	2008	Abstract.
Wright	2009	Not the strategy of air purification.
Stillerman	2010	Treatment of rhinitis.
Moffatt	2011	Abstract.
Mohan	2011	Abstract.
Takaro	2011	Not a RCT.
Ho	2012	Abstract.
Yunus	2012	Abstract.
Hogaard	2014	Abstract.
Nct	2014	Not a RCT.
Nct	2014	Not a RCT.
Hogaard	2014	Abstract.
Gore	2015	Not a RCT.
Vijayan	2016	Not a RCT.
Storrar	2016	Not a RCT.
Luo	2017	Abstract.
Miyoshi	2018	Abstract.
Bjermer	2019	Not a RCT (post-hoc analysis).

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