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REVIEW

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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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Summary

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.

KEYWORDS

allergens, asthma, environment, house dust mite allergen control, strategy of avoidance

1 | 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.

2 | STRATEGIES FOR MITE ALLERGEN CONTROL

2.1 | 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]

2.2 | 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 simple colorimetric 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.

2.3 | 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 10-40 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]

2.4 | 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.

3 | EVIDENCE SUPPORTING THE STRATEGIES

3.1 | 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[40] attempted to study the effects of feather bedding, but the selected trials did not meet the inclusion criteria. 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 and Jaiswal 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]

3.2 | 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.

4 | THE POSSIBLE ROLES OF STRATEGIES IN EFFECTIVENESS: AN EXAMPLE

4.1 | 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[27]).

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]

4.2 | 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; Refs. 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%-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%-28%; Table 3). Three subgroups reported on PC_{20} outcome, with the SMD ranging from −0.12 to +0.05 (*P* = 0.45-0.80; Table 4). The subgroups showed no heterogeneity (I^2 = 0%). For medication usage, two subgroups reported an SMD = −0.04 to −0.17 (*P* = 0.46-0.49; I^2 = 0%; Table 5). The risk ratio for the number improved in the subgroups of concurrent bedroom interventions was 0.85-1.07 (*P* = 0.77-0.87), 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.

4.3 | 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]

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	

5 | GENERAL DISCUSSION

5.1 | 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]

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	0.14	−0.02 to 0.29	633	0.08	0%
1 barrier	0.11	−0.11 to 0.33	332	0.32	0%
2-3 barriers	0.17	−0.06 to 0.40	301	0.15	28%
Air purification	0.07	−0.53 to 0.68	42	0.81	0%
Mixed strategies	0.13	−0.02 to 0.29	675	0.09	0%
Gøtzsche & Johansen[a]	0.13	−0.02 to 0.28	675	0.09	0%

[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.

5.2 | 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]

5.3 | Recent studies

Additionally, recent studies have not related their findings to a specific strategy. Leas et al[91] systematically reviewed the effectiveness of

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	0.75-1.50	282	0.82	0%
1 barrier	1.07	0.75-1.53	233	0.77	0%
2-3 barriers	0.85	0.19-3.79	49	0.87	0%
Air purification	0.67	0.24-1.87	56	0.61	0%
Mixed strategies	1.01	0.73-1.40	338	0.96	0%
Gøtzsche & Johansen[a]	1.01	0.80-1.27	338	0.94	0%

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

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.

5.4 | 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.

5.5 | 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.

6 | 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.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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