

REVIEW

Effectiveness of mite-impermeable covers: a hypothesis-generating meta-analysis

F. E. van Boven

Working Group on Allergen Avoidance, V&VN Lung Care Nurses, V&VN Dutch Nurses' Association, Utrecht, The Netherlands

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Summary

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. 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. Twelve trials included 1187 observations. The interventions included one barrier or product (six trials), two barriers or partial control (four trials) and three barriers or integral control (two 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 $\mu\text{g/g}$; $P = 0.02$). Changes in load showed similar tendencies. Health outcomes showed moderate to considerable heterogeneity (physiological outcomes $I^2 = 44$ – 94% ; symptom score $I^2 = 93\%$). 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.

Correspondence:

F. E. van Boven, Boomheide 4, 3069 LA Rotterdam, The Netherlands.

E-mail: f.vanboven5@gmail.com

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Introduction

Asthma is a disorder of the conducting airways characterized by heterogeneity in immunopathology, phenotypes, response to therapies and patient history [1]. The first-line therapies for the treatment of allergic asthma include the following: immunotherapy, drug therapy and environmental exposure control. The topic of mite allergen control has developed into a debate. At the highest level of evidence, Gøtzsche and Johansen [2] concluded that chemical and physical methods aimed at reducing exposure to house dust-mite allergens could not be recommended. The rigorous and robust meta-analysis by Gøtzsche and Johansen [2] has garnered nearly two hundred citations (Google Scholar, retrieved July 4, 2014) and is being discussed in a number of

other channels [3–7]. As a result of this debate, modern guidelines provide ambiguous recommendations for mite control [8, 9].

A not well-discussed aspect of their study is the selection by Gøtzsche and Johansen [2] of a 'univariate' meta-analysis including 52 trials of various types of interventions. A strategic intervention yields an assessment of all of the sources of exposure [10]; however, the paradigm regarding the contribution of mite allergens to airway disease relates to the bedding [11]. An environmental framework of mite allergen control, with bedding control as the primary barrier, is offered by Colloff [12] as follows:

- 1 Fit mite-impermeable covers to all of the bedding elements (barrier 1).

- 2 Launder bedding monthly with hot water, with a minimum temperature of 60°C (barrier 2).
- 3 Remove or clean bedroom carpet and soft toys (barrier 3).

In this study, the fitting of covers to all of the bedding elements, that is, the mattress, duvet and pillow, is defined as 'full-cover technology'. The use of only the first barrier is a 'product' and the use of two barriers is defined as 'partial bedding control'. Three or more barriers are defined as 'integral bedding control'.

An important initial question in a review of the interventions is whether varying the intervention substantially affects the health outcomes and whether restrictions on such variations might be important [13]. The effects of variations in the intervention are analysed by regression. The potential consequence of a meta-regression based on a few trials is data dredging [14]. It is recommended that the primary aim in investigating the effects of covariates is to define the protocol. This study continues the meta-analysis by Gøtzsche and Johansen [2] to generate hypotheses on the effectiveness of varying bedding interventions for the treatment of allergic asthma. The interventions are limited to full-cover technology.

Methods

Search strategy and the selection of studies

The basis of this meta-analysis was the Cochrane review by Gøtzsche and Johansen [2]. This review was up-to-date until 11 July 2011 and includes 52 trials on mite allergen control. A subgroup of 26 trials reported the clinical effects after bedding control. The reports included in this study were limited to publications in English, and abstracts were excluded. Only reports on full-cover technology were included. Eleven authors were contacted twice for missing values. None of the correspondents provided additional data. An additional search was performed in PubMed using the keywords 'mite* AND asthma*', combined with 'random* OR control* OR blind*'. The search was performed for new randomized trials on the treatment of asthma that were published from 1 July 2011 through 4 July 2014.

Data extraction

The following outcome measures were extracted:

General and explanatory outcomes:

- 1 Sample size.
- 2 Type of barrier(s) used.
- 3 Mite allergen load from the mattress ($\mu\text{g/g}$).
- 4 Type of patient (child or adult).
- 5 Use of steroids at baseline (yes or no).

- 6 Judgement regarding allocation concealment by Gøtzsche and Johansen (high, low and unclear risk).

Clinical outcomes:

- 7 Asthma symptom score.

Physiological outcomes (primary and secondary):

- 8 Percentage of predicted FEV₁ (forced expiratory volume in 1-s).
- 9 PC₂₀ (provocative concentration that causes a 20% fall in FEV₁).
- 10 PEFR (peak expiratory flow rate).

The interventions and control measures were judged for the type of bedding intervention used. In cases in which a barrier met the criteria of 'complete', it was coded as '1'. The methods describing the absence of barriers or unclear interventions were coded as '0'. No corrections were made for possible compensation between barriers.

After judging the barriers, the outcomes for the baseline, final and change were extracted, including the point estimator and the standard deviation. The first-line point estimator was the mean. In cases in which a trial included additional types of interventions, the groups were not combined because this analysis was not the aim of this study. The first-line treatment was integral control. In cases in which the extracted data differed from the data extracted by Gøtzsche and Johansen [2], the differences were listed. For mite load, FEV₁ and peak flow, the change was extracted. The final values were extracted for the mite load, PC₂₀ and asthma symptom scores. The direction of changes was defined as positive for increasing the FEV₁ and peak flow (final – baseline) concurrent to decreasing the mite load (baseline – final). In the case of missing values for the standard deviation of the final values, they were established as equal to the baseline values. The standard deviation of the change was calculated by imputation, with the correlation coefficient set to $\rho = 0.5$. The remaining data with missing values were excluded from the analysis.

Statistical and sensitivity analysis

The effect size for this study was the standardized mean difference. First, the covariate risk of bias, the type of patient and the use of steroids at baseline were tested for possible confounding of the outcomes. With a positive result for confounding, the possibility of correction was considered. Further analysis was performed while adjusting for the covariate baseline load, the type of intervention or the interaction between the baseline load and the type of intervention. In the latter, the type of intervention was represented by the number of barriers.

ers used. The interaction term was introduced by the square root without intercept, to test the hypothetical non-linear tendency of changes in the mite load. Models without intercept were used to test the covariate baseline load, whereas a negative mite load at baseline was expected to result in a negative load outcome. The health outcomes were tested with an intercept. A random-effects model was used for estimating the overall effect from all the trials. Mixed-effects meta-regression models were used for a preferred minimum of ten trials [13]; however, these models were not employed for five or fewer trials to avoid the risk of over-fitting. The Knapp and Hartung adjustment [17] was introduced in cases of a small number of trials and if heterogeneity were present. The calculations yielded the I-squared for testing the heterogeneity, the overall mean estimate, the F-statistic and estimates for the mixed-effects models. All of the calculations were performed with the metafor package 1.9.1 [18] in R (version 3.0.2).

A sensitivity analysis was performed to determine whether the selection of a correlation coefficient $\rho = 0.5$ for the imputation of the standard deviation affected results. The analysis was repeated with $\rho = 0.3$, $\rho = 0.7$ and $\rho = U$ (0.3–0.7) by random sampling from the uniform distribution. The latter was simulated in R using `set.seed(1)`. Additionally, the sensitivity analysis yielded the repetition of some alternatives by Gøtzsche and Johansen [2], who excluded the trial by Thiam [19]. When the interaction term was positive, the sensitivity was tested by the weight product = 1, partial = 1.5 and integral = 1.7. The multiple positive covariates were tested for collinearity by calculating the maximum condition number Φ .

Treatment of methodological bias

The 52 reviewed trials were previously evaluated regarding the risk of bias about the allocation concealment by Gøtzsche and Johansen (high risk, low risk or unclear risk) [2]. Additionally, the potential for outcome reporting bias was judged previously [2] and was determined to be high. New trials were judged by the author when they were included for analysis. Because only publications in English were included in this study, a language bias was introduced. However, according to the abstracts and characteristics collected by Gøtzsche and Johansen [2], none of the excluded trials in other languages yielded integral control.

Results

Selected studies and characteristics

Gøtzsche and Johansen [2] judged 19 trials including impermeable covers as appropriate for inclusion in their

meta-analysis. One publication was excluded due to the absence of English text [20]. Two trials did not report on impermeable covers [21, 22]. Four trials did not report on full-cover technology [23–26]. The health data from one trial were judged not useful by Gøtzsche and Johansen [27]. The data of one trial did not allow for extracting data on the mite load [28]. Two trials were excluded partly because of missing values (mite load and change in PEFR [16] and mite load [29]).

All of the new trials did not include full-cover technology and were excluded [30–35]. Data were extracted from 12 trials [15, 16, 19, 28, 29, 36–42]. Six trials included the use of a product, four trials included partial control and two small trials included integral control (Table 1). Study designs included parallel group studies, crossover studies and combined methods. The trials reported on children or adults, and the length of interventions varied from 4 weeks to 2 years. The total number of observations was 1187.

Exposure outcomes

The final load data demonstrated considerable heterogeneity ($I^2 = 93\%$, 95% CI: 83% to 98%) for the random-effects model (Table 2). The standardized mean difference for the final load was significant ($P = 0.004$). Judgement on the allocation was positive ($F_{df1=1; df2=7} = 6.48$ ($P = 0.04$; Fig. 1a). Influence diagnostics indicated that the trial by Cloosterman [36] was the most influential ($r_{\text{student}} = -2.57$; Cook's $d = 2.03$). The mixed-effect models for environmental covariates indicated positive results for the covariate baseline load ($P = 0.03$) and the square root of the interaction term ($P = 0.02$; Fig. 1b). The covariate type of intervention indicated negative results ($F_{df1=2; df2=6} = 0.29$ ($P = 0.76$). Influence diagnostics indicated that the trial by Rijssenbeek [41] was the most influential (Cook's $d = 0.12$, $\text{hat} = 0.37$).

The reduction in heterogeneity was to the category substantial ($I^2 = 80\%$, 95% CI: 50% to 97%; six trials) after excluding the three trials with a judgement of high risk of bias about allocation. The standardized mean difference for the final load was significant ($P = 0.02$). Heterogeneity decreased in the mixed-effect model with the covariate square root of the interaction ($I^2 = 69\%$), whereas the covariate square root of the interaction increased in significance ($P = 0.004$).

Changes in the mite load demonstrated considerable heterogeneity ($I^2 = 91\%$, 95% CI: 79% to 97%). The standardized mean difference for the change in the load was significant ($P = 0.01$). The mixed-effect models demonstrated that the square root of the interaction term influenced the outcomes ($P = 0.05$). Again, influence diagnostics indicated that the trial by Rijssenbeek [41] was most influential ($\text{hat} = 0.36$). The covariate

Table 1. Characteristics of studies included in the meta-analysis

Trial	Type of bedding intervention	Overall mean baseline load ($\mu\text{g/g}$)	Type of patient	Use of steroids at baseline	Judgement on risk of bias about allocation concealment by Gøtzsche and Johansen [2]	Health outcomes extracted	Remarks/differences with extractions by Gøtzsche and Johansen [2]
Carswell [15]	Integral	0.44	Child	Yes	Unclear	FEV ₁ and PEFR	Estimations used at period of 24 weeks
Cloosterman [36]	Partial	0.90	Adult	No	High	FEV ₁ , PC ₂₀ , PEFR and symptoms	Endline log (PC ₂₀) for treatment: -0.37 , control $+0.08$ mg/mL
De Vries [16]	Product	0.8	Adult	Yes	High	PEFR and symptoms	Symptom scores obtained at a period of 2 years, SD from extractions by [2] mite load and change in PEFR excluded due to missing values
Dharmage [37]	Product	19.05	Adult	No	High	Symptoms	Use of night symptom scores instead of daytime scores (the median of the daytime at baseline for treatments was zero)
Ehnert [38]	Partial	16.0	Child	Yes	Unclear	PC ₂₀	
Luczynska [39]	Product	22.07	Adult	Yes	High	PEFR	
Marks [40]	Partial	20.75	Adult	Yes	Unclear	FEV ₁ , PC ₂₀ and symptoms	
Rijssenbeek [41]	Integral	24.64	Adult	No	Unclear	PC ₂₀ , PEFR and symptoms	Log (PC ₂₀) used from extractions by [2]
Sheikh [28]	Product	NA	Child	Yes	Low	PEFR and symptoms	
Thiam [19]	Partial	2	Child	Yes	Unclear	FEV ₁ and symptoms	
Van den Bemt [42]	Product	4.22	Adult	Yes	Unclear	PEFR	
Woodcock [29]	Product	1.4	Adult	Yes	Low	PEFR and symptoms	SD for outcomes not applicable, used from extractions by [2] Mite load excluded

Table 2. Grouped results of the meta-regression on mite load data by various covariates and subgroups

Confounder/covariate	Subgroup	Final load		Change in load	
		Trials (n)	95% CI mean difference	Trials (n)	95% CI mean difference
-		9	-3.12 to -0.86	9	0.46 to 2.31
Judgement on risk				9	NS
	High risk of allocation	3	-4.91 to -1.81		
	Unclear risk of allocation	6	-2.42 to -0.21		
Baseline load		9	-0.20 to -0.01	9	-0.02 to 0.14
Type of intervention		9	NS	9	NS
	Product				
	Partial control				
	Integral control				
Square route of interaction		9	-0.66 to -0.07	9	0.00 to 0.48
Multiple model	Judgement on risk: unclear	6	-0.43 to -0.14	6	-0.03 to 0.51
	Judgement on risk: high	9	-4.93 to -1.41	9	-0.67 to 3.45
	Judgement on risk: unclear		-2.58 to 0.67		-0.54 to 3.36
	Interaction		-0.06 to 0.03		-0.05 to 0.05

NS, not significant.

Bold = (approaching) significance.

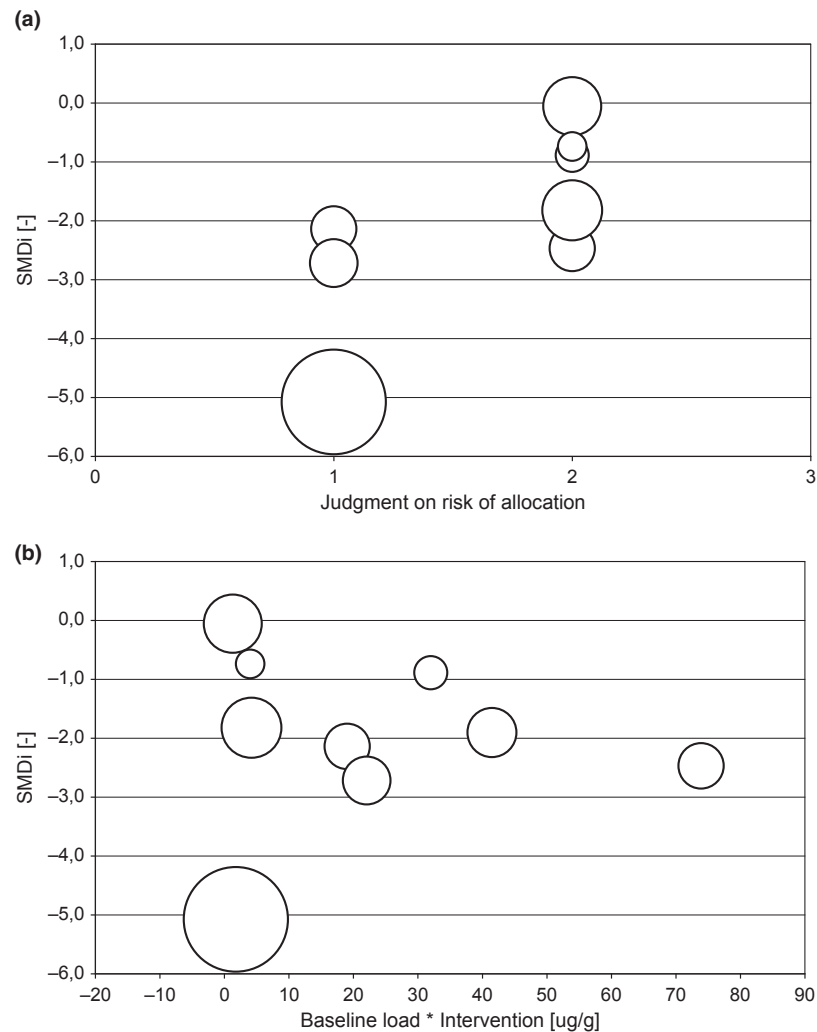


Fig. 1. L'Abbé-plots of standardized mean difference (SMD) for final load: (a) SMD vs. judgement on the risk of allocation concealment (1 = high risk; 2 = unclear risk); (b) SMD vs. interaction term (baseline load * number of barriers used).

square root of the interaction continued to approach significance after excluding the trials with a judgement of high risk of bias about allocation ($P = 0.07$).

Physiological outcomes

Random-effects models showed substantial heterogeneity for the FEV₁ data ($I^2 = 71\%$) and moderate heterogeneity for the PC₂₀ data ($I^2 = 44\%$). However, the confidence intervals were very wide (95% CI: 3% to 99%, respectively, 0% to 95%). The Q-test for heterogeneity was significant for the model of FEV₁ ($P = 0.02$), whereas it nearly approached significance for PC₂₀ ($P = 0.11$).

The standardized mean effects for FEV₁ and PC₂₀ were not significant (respectively, $P = 0.20$ and $P = 0.33$, Table 3, Fig. 2). Heterogeneity in FEV₁ was reduced to moderate ($I^2 = 46\%$) after excluding one trial with a judgement of high risk of bias about allocation.

After excluding the trial of Thiam [19], no heterogeneity was further observed in the data for FEV₁ (two trials). The exclusion of two trials with a high risk of bias also eliminated heterogeneity in PC₂₀ ($I^2 = 0\%$; three trials). The trial by Carswell [15] was the most influential regarding the data on FEV₁ (Cook's $d = 1.2$, $\text{hat} = 0.4$), whereas the trial by Marks [40] influenced PC₂₀ the most (Cook's $d = 0.75$, $\text{hat} = 0.4$) (Fig. 3).

The data regarding PEFR demonstrated considerable heterogeneity ($I^2 = 94\%$, 95% CI: 85% to 99%). Heterogeneity was highly positive ($P < 0.0001$) by use of the Q-test. The standardized mean effect was not significant ($P = 0.25$). After excluding trials with a high risk of bias, the five remaining trials showed considerable heterogeneity ($I^2 = 94\%$). The level of significance of the standardized mean differences was not altered. The data by Van den Bemt [42] influenced PEFR the most ($r_{\text{student}} = 4$, Cook's $d = 1$) (Fig. 4).

Table 3. Grouped results of the meta-regression on health outcomes by various covariates and confounders

Confounder/covariate	Subgroup	FEV ₁		PC ₂₀		PEFR		Asthma symptom score	
		Trials (n)	95% CI mean difference	Trials (n)	95% CI mean difference	Trials (n)	95% CI mean difference	Trials (n)	95% CI mean difference
–		4	–0.53 to 1.65	5	–0.32 to 0.75	7	–0.42 to 1.32	8	–1.13 to 0.45
Judgement on risk		4	NA	5	NA	7	NS	8	NS
	High risk of allocation								
	Unclear risk of allocation	3	–0.87 to 2.44	3	–0.64 to 1.49	5	–0.65 to 1.98	5	–1.93 to 1.33
	Low risk of allocation								
Type of patient		4	NA	5	NA	7	NS		
	Child							2	–2.93 to 0.18
	Adult							6	–0.84 to 0.70
Use of steroids		4	NA	5	NA	7	NS	8	NS
	No								
	Yes								
Baseline load		4	NA	5	NA	6	NS	7	NS
Type of intervention		4	NA	5	NA	7	NS	8	NS
Square route of interaction		4	NA	5	NA	6	NS	7	NS

NS, not significant; NA, not applicable/not calculated.

Bold = (approaching) significance.

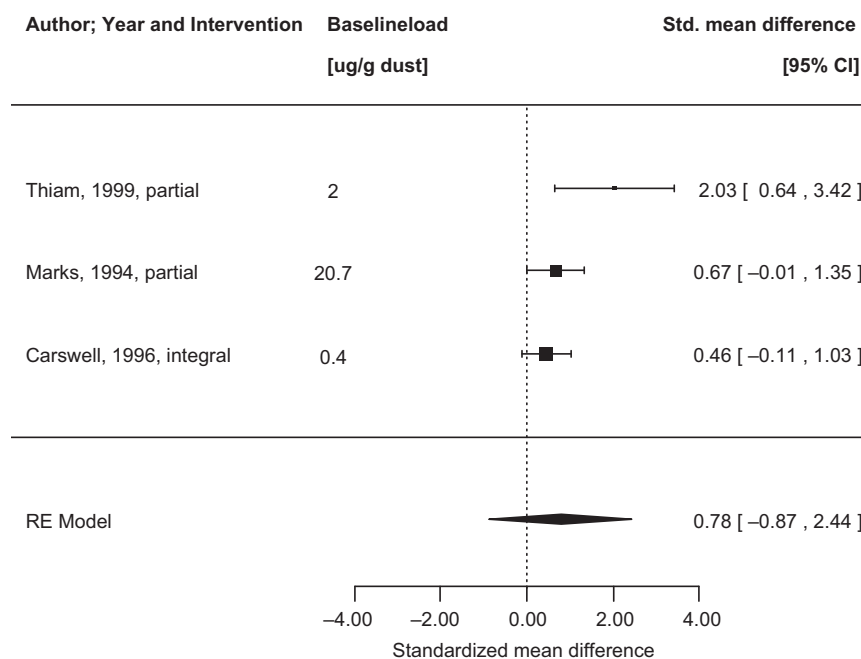


Fig. 2. Forest plot of the standardized mean differences with a 95% confidence interval (CI) for the change in FEV₁ based on a random-effects model and the exclusion of trials with high risk of bias.

Clinical outcomes

Asthma symptoms showed considerable heterogeneity ($I^2 = 93\%$, 95% CI: 82% to 99%; Table 3). The Q-test for heterogeneity was highly positive ($P < 0.0001$). The stan-

dardized mean difference was not significant ($P = 0.34$, Fig. 5). The mixed-effects models showed an increased F-statistic for the type of patient ($F_{df1=1;df2=6} = 3.38$; $P = 0.12$). The omnibus model demonstrated a higher standardized mean difference for children, and this result

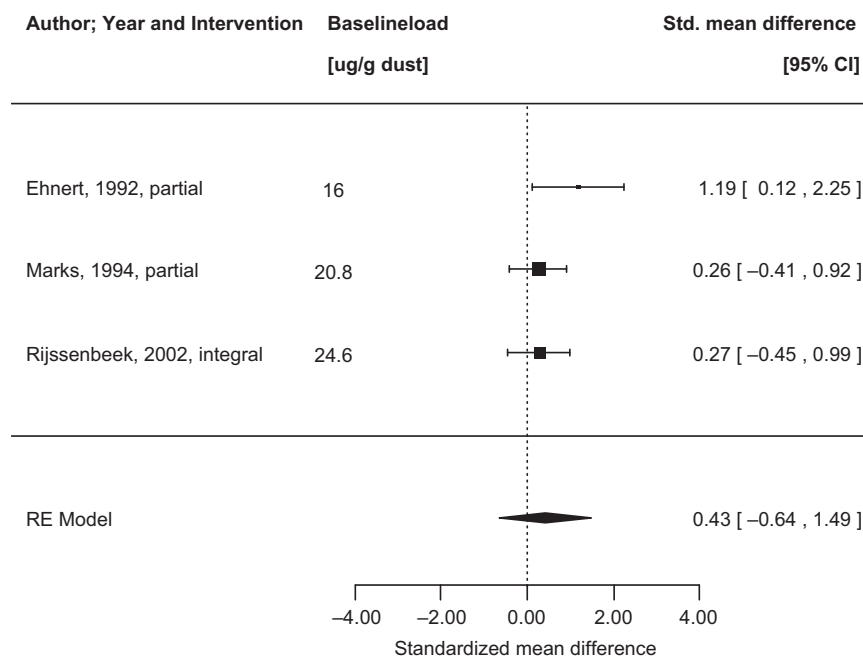


Fig. 3. Forest plot of the standardized mean differences with a 95% confidence interval (CI) for the final value of PC₂₀, based on a random-effect model and the exclusion of trials with high risk of bias.

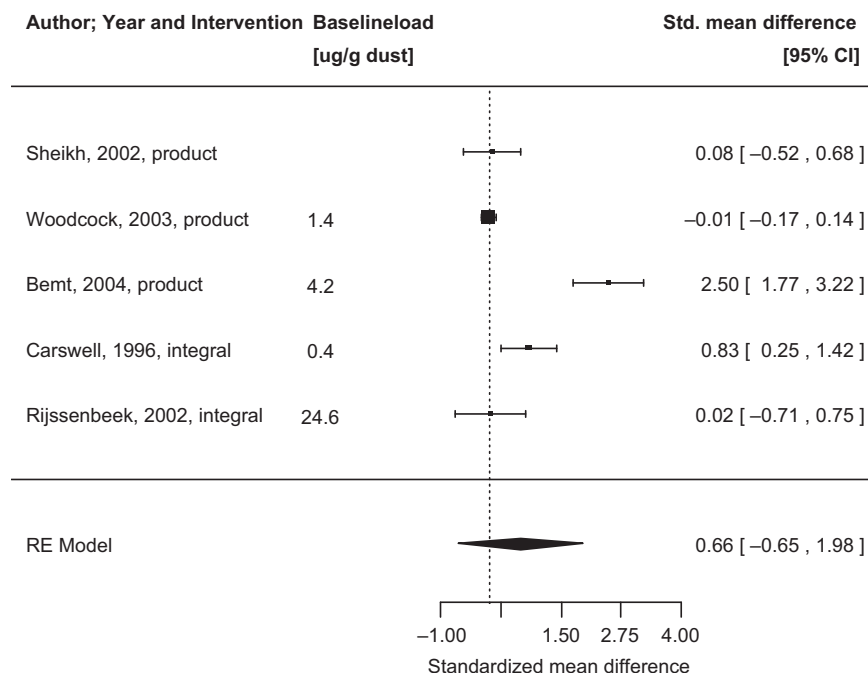


Fig. 4. Forest plot of the standardized mean differences with a 95% confidence interval (CI) for the change in PEFR, based on a random-effect model and the exclusion of trials with high risk of bias.

approached significance ($P = 0.07$). Heterogeneity was still considerable ($I^2 = 94\%$) after correcting the data set for the trials with a high risk of bias. The trial by Thiam [19] was most influential due to Cook's d (0.5). Exclusion of the trial by Thiam [19] reduced heterogeneity by another 5%.

Sensitivity analysis

The results for the data imputed with $\rho = 0.30$, 0.70 and random sampling did not alter the trends in the calculations. Changing the weight of the type of intervention did not alter the results of the mite load for the

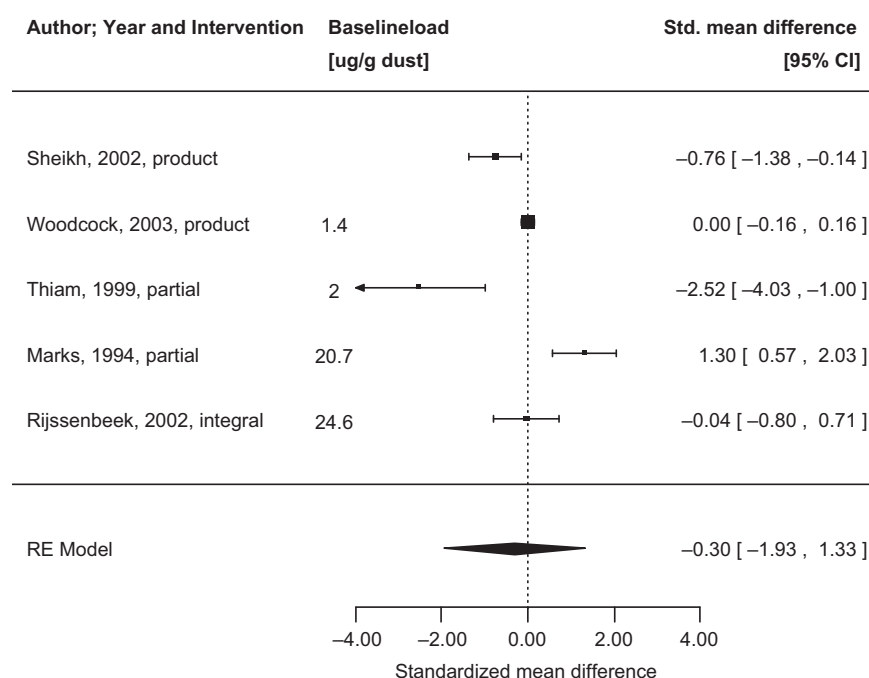


Fig. 5. Forest plot of the standardized mean differences with a 95% confidence interval (CI) for the final asthma symptom scores, based on a random-effect model and the exclusion of trials with high risk of bias.

influence of the interaction. The maximum condition number of the correlation matrix with positive covariates was calculated as $\Phi_{\text{baseline load vs risk of bias}} = 1.65$.

Discussion

This study continues the meta-analysis on mite control that was started by Gøtzsche and Johansen [2]; this study examines different types of bedding interventions. Bedding interventions were limited to full-cover technology and were examined by the use of meta-regression. Gøtzsche and Johansen [2] used a 'univariate' meta-analysis. The results of the present study indicate that the final load is influenced by the risk of bias and also by the interaction between the baseline load and the type of intervention. The latter is particularly influential when the baseline load is high, although this calculation was underpowered. Calculations of the change in mite load showed similar results for the interaction term, although the results only approached significance. There were no signs of collinearity between significant covariates. The health outcome analyses showed moderate to considerable heterogeneity with large uncertainty for heterogeneity in FEV₁ and PC₂₀. The latter was due to the small number of trials available. The overall mean effects were observed to be negative for all of the health outcomes. Environmental covariates did not influence the peak flow or asthma symptoms. The results for the peak flow and asthma symptoms confirm a recent conclusion by

Wright [43] that the use of products are not effective, whereas the number of trials aiming at a substantial reduction in the mite load are sparse and small in size. However, these results do not confirm the conclusions by Gøtzsche and Johansen [2] that mite control does not result in a clinical benefit. Contrary to the results of this study, Gøtzsche and Johansen [2] did not detect heterogeneity for any of the outcomes ($I^2 = 0$) except the asthma symptom scores ($I^2 = 61\%$). Nonetheless, the total number of trials in this study was small, and the calculations appear likely to be underpowered. This fact emphasizes the recommendation by Thomson [14] to use this study for achieving the objective of hypothesis generation.

Two types of adjustments were included in this study. The first adjustment comprises the baseline outcomes. The other type of adjustment involves introducing covariates. With regard to the first type, the baseline, final and change values were extracted in this study. Gøtzsche and Johansen [2] did not adjust for baseline differences to avoid the risk of selection bias. Furthermore, when evaluating the data extracted by Gøtzsche and Johansen [2], it appeared that in the majority of cases, the final or follow-up values were reported, at the same time including some change values. The choice of reporting the change or the final value is complicated. The statistical preference is to adjust using analysis of covariance (ANCOVA), regardless of the imbalance in the baseline data [44]. However, the extracted data did not allow for ANCOVA. When the correlation

between the baseline and final values is likely to be strong ($\rho \geq 0.7$), the change estimate has a similar power compared with the ANCOVA estimate [44]. Otherwise, final values are preferred. An analysis of individual patient data presented by Rijssenbeek [41] indicates strong correlations between baseline and final values due to morning peak flow (CI: 0.92 to 0.99 for treatment and 0.65 to 0.96 for controls) and moderate correlations due to asthma symptom score (CI: 0.37 to 0.92 for treatment and 0.06 to 0.86 for controls). In general, when the magnitude of the baseline value is considerably larger than the expected change, strong correlations might be expected and reporting changes are preferred over final values. This is the case with the FEV₁, PEFR and high baseline load combined with substantial reductions.

The other type of adjustment comprises the environmental characteristics. The two trials on integral control highlight the relevance of differences in the baseline mite load. Among all of the types of interventions, the baseline load reported by Carswell [15] and Rijssenbeek [41] differed tremendously. Systematic differences in the baseline characteristics might be associated with selection bias [13]. This judgement appears to play a small role in this study, whereas the judgement on the allocation partly explained the heterogeneity in the final exposure outcomes (13%). The results indicate that the baseline load and the type of intervention both influenced exposure outcomes, even after the elimination of trials with a high risk of bias. Of importance in this case is whether there is prior knowledge of an influencing covariate [45]. The prior knowledge of environmental covariates relates to two rationales. One rationale is the paradigm for the hygienic limits [11], reflecting the existence of a dose-response relationship with mite load rather than with independent asthma outcomes. The other rationale is described by Colloff [12] and reflects on the principles of integrated pest management by incorporating the synergistic effects of barriers. To explore the effectiveness of synergistic effects, it is of particular interest to examine the data on integral control. Carswell [15] reported a mite load at an acceptable baseline level. The mite load was reduced to zero by the use of integral control. With regard to the paradigm on the hygienic limit, it is unlikely that the reduction achieved by Carswell fully explained the improvements in the asthma outcomes. Therefore, and as in this study, the small trial by Rijssenbeek [41] on integral control is likely to be the only trial of relevance for the examination of asthma outcomes.

The presence of substantial or considerable heterogeneity ($I^2 > 80\%$) in almost all of the outcomes reflects that more variation is observed than would be expected due to chance. The covariates examined in this study only explained a small part of the observed heterogeneity,

indicating that not all of the possible explanatory variables were investigated. It appears likely that known pathological sources as described by Holgate [1] also play a role in understanding clinical trends in bedding interventions.

Many other investigators have discussed the meta-analysis by Gøtzsche and Johansen [3–7]. None of the authors presented data to the contrary with a similar level of evidence. Pingitore [7] noted that trials that were not able to obtain a decrease in the exposure level should not be included in the meta-analysis. However, in an earlier version (2004), Gøtzsche and Johansen [2] reported a subgroup analysis on successful mite reduction, showing similar results. This subgroup of successful mite reduction was based on a decreasing mite load due to chance rather than an environmental reason for the decrease. Two other studies have been reported on effectiveness of mite covers with a similar level of evidence. Recer [46] found modest effectiveness for mite covers when the baseline mite load was above the hygienic limit. However, Recer [46] used a statistical method uncommon in systematic reviewing, comparing treatment with control in an indirect manner. A recent meta-analysis on mite-impermeable covers [47] demonstrates weaknesses due to the use of the same statistical approach used by Gøtzsche and Johansen [2]. The results obtained by this *post hoc* meta-regression challenge the conclusions drawn by Gøtzsche and Johansen [2], with an equivalent level of evidence.

This meta-regression on bedding control indicates that integral control reduced the mite load the most when the load was high at baseline. The number of trials on integral control was too small to allow for an appropriate examination of health outcomes. At the highest level of evidence, we are unable to draw conclusions on the clinical effectiveness of bedding control. There is an urge for new trials examining substantial reductions in the mite load when the load is high at baseline (e.g. integral control). Future studies are suggested to test the hypothesis that patients with allergic asthma benefit from interventions that substantially reduce bedding exposure when the mite load is high at baseline. Guidelines should reflect a reversal in the level of evidence regarding mite allergen bedding control.

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Conflict of interests

The authors declare no conflict of interest.

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