Preventing Severe Asthma Exacerbations in Children
A Randomized Trial of Mite-Impermeable Bedcovers

Clare S. Murray[1,2,3], Philip Foden[1,2], Helen Sumner[1], Elizabeth Shepley[1,2,4], Adnan Custovic[5], and Angela Simpson[1,2]

[1]Division of Infection, Immunity and Respiratory Medicine, Manchester Academic Health Sciences Centre, University of Manchester, Manchester, United Kingdom; [2]University Hospital of South Manchester, Manchester, United Kingdom; [3]Royal Manchester Children's Hospital, Central Manchester University Hospitals National Health Service Foundation Trust, Manchester, United Kingdom; [4]National Institute for Health Research South Manchester Respiratory and Allergy Clinical Research Facility, University Hospital of South Manchester, United Kingdom; and [5]Department of Paediatrics, Imperial College London, London, United Kingdom

ORCID ID: 0000-0003-2733-6666 (A.S.).

Abstract

Rationale: Allergen exposure in sensitized individuals with asthma interacts with viruses to increase the risk of asthma exacerbation.

Objectives: To evaluate the use of house dust mite–impermeable bedding and its impact on severe asthma exacerbations in children.

Methods: We randomized mite-sensitized children with asthma (ages 3–17 yr) after an emergency hospital attendance with an asthma exacerbation to receive mite-impermeable (active group) or control (placebo group) bed encasings.

Measurements and Main Results: Over a 12-month intervention period, the occurrence of severe asthma exacerbations was investigated. Of 434 children with asthma who consented, 286 (mean age, 7.7 yr; male sex, 65.8%) were mite sensitized, and 284 were randomized (146 to the active group and 138 to the placebo group). At 12 months, significantly fewer children in the active group than in the placebo group had attended the hospital with an exacerbation (36 [29.3%] of 123 vs. 49 [41.5%] of 118; $P = 0.047$). In the multivariable analysis, the risk of emergency hospital attendance was 45% lower in the active group (hazard ratio, 0.55; 95% confidence interval [CI], 0.36–0.85; $P = 0.006$) than in the placebo group. The annual rate of emergency hospital attendance with exacerbations was 27% lower in the active group than in the placebo group, but this did not reach significance (estimated marginal mean [95% CI], active, 0.38 [0.26–0.56] vs. placebo, 0.52 [0.35–0.76]; $P = 0.18$). No difference between the groups in the risk of prednisolone use for exacerbation was found (hazard ratio, 0.82; 95% CI, 0.58–1.17; $P = 0.28$).

Conclusions: Mite-impermeable encasings are effective in reducing the number of mite-sensitized children with asthma attending the hospital with asthma exacerbations but not the number requiring oral prednisolone. This simple measure may reduce the health care burden of asthma exacerbations in children.

Clinical trial registered with www.isrctn.com (ISRCTN 69543196).

Keywords: asthma; exacerbations; allergens; avoidance; child

(Received in original form September 30, 2016; accepted in final form February 21, 2017)

Supported by the J. P. Moulton Charitable Foundation. Infrastructure support was provided by the North West Lung Centre Charity. Neither the funders nor sponsors of the study, nor the manufacturers from whom the encasings were purchased, had any role in the study design, data collection, data analysis, data interpretation, or writing of the report.

Author Contributions: Full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis: C.S.M. and A.S.; study concept and design: C.S.M., A.S., and A.C.; acquisition, analysis, or interpretation of data: C.S.M., A.S., A.C., H.S., P.F., and E.S.; drafting of the manuscript: C.S.M. and A.S.; critical revision of the manuscript for important intellectual content: C.S.M., A.S., A.C., H.S., P.F., and E.S.; statistical analysis: P.F.; obtained funding: C.S.M., A.S., and A.C.; administrative, technical, or material support: H.S. and E.S.; and study supervision: C.S.M. and A.S.

Correspondence and requests for reprints should be addressed to Clare S. Murray, M.D., Division of Infection, Immunity and Respiratory Medicine, Faculty of Biology, Medicine and Health, School of Biological Sciences, University of Manchester, 2nd Floor, Education and Research Building, University Hospital of South Manchester, Southmoor Road, Manchester M23 9LT, UK. E-mail: clare.murray@manchester.ac.uk

This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org

Am J Respir Crit Care Med Vol 196, Iss 2, pp 150–158, Jul 15, 2017

Originally Published in Press as DOI: 10.1164/rccm.201609-1966OC on March 10, 2017
Internet address: www.atsjournals.org

At a Glance Commentary

Scientific Knowledge on the Subject: Asthma exacerbations in children are a leading cause of hospitalization. Exposure in sensitized individuals, in synergy with viral infections, greatly increases hospital admission risk. In the developed world, the house dust mite is the commonest sensitizing allergen. In no studies done to date have researchers investigated the effect of allergen avoidance on asthma exacerbations and hospital admissions in children.

What This Study Adds to the Field: The use of mite-impermeable bedding for mite-sensitized children with asthma can significantly reduce the risk of severe exacerbations that would result in emergency hospital attendance.

Asthma is the most common chronic disease in childhood. Although asthma in most children is well controlled with pharmacotherapies, a significant number of children experience exacerbations, which remain one of the commonest reasons for pediatric hospital admission in the developed world (1). This unscheduled care accounts for a large proportion of asthma costs, and a single exacerbation can increase annual costs more than threefold (2). Previous hospital admissions predict future hospitalizations (3). Respiratory viral infections are major risk factors for hospital admission (4–6), particularly among children who are exposed to allergens to which they are sensitized, where these factors act synergistically to markedly increase the risk of hospital admission (7, 8). However, disrupting this interaction in individuals with atopic asthma is challenging.

There are currently no available vaccines for viruses that cause the majority of exacerbations. Allergen-specific immunotherapy is generally not recommended for patients with uncontrolled asthma (9). Anti-IgE monoclonal antibody (omalizumab) can reduce asthma exacerbations, but its use is limited to the most severe cases of asthma because of high cost and requirement for regular injections (10). Avoidance of allergen remains a potentially cost-effective intervention. However, to our knowledge, no studies to date have investigated the effect of allergen avoidance on asthma exacerbations and hospital admissions; instead, studies have been focused on symptom scores, medication use, and lung function.

House dust mite (HDM) is a common allergen linked to expression of asthma, with up to 65% of U.K. children with asthma demonstrating sensitization (7). Although high HDM exposure has been linked to asthma severity (11), authors of a meta-analysis of 44 trials of mite avoidance were unable to demonstrate any clinical benefit of measures designed to reduce mite exposure, and they concluded that mite control measures could not be recommended for asthma (12). However, this meta-analysis included many studies where no exposure reduction was achieved, and the authors did not distinguish between adult and pediatric studies. Indeed, most studies that suggest benefits of mite avoidance have been conducted in children (13–17). However, these studies were either small (13, 15, 17); used multifaceted interventions, making blinding difficult (13, 17); targeted multiple allergens (14, 16); or were conducted in populations that have poor access to health care/medications (14, 16). Given the evidence of a synergism between viral infection and allergen exposure in increasing the risk of asthma exacerbations in sensitized individuals (7, 18), we hypothesized that effective reduction in mite exposure might reduce the risk of exacerbations in these patients.

In the present double-blind study, Preventing Asthma Exacerbations by Avoiding Mite Allergen (PAXAMA), we compared the effect of mite-impermeable bedcovers with that of placebo bedcovers in reducing the risk of severe asthma exacerbations in mite-sensitized children with asthma who had recently attended the hospital with an asthma exacerbation. Some of the results of these studies were previously reported in the form of an abstract (19).

Methods

Study Design

This randomized, double-blind, placebo-controlled, parallel-group study of the effect of mite-impermeable bedcovers on the risk of severe asthma exacerbations in mite-sensitized children with asthma was conducted across 14 hospitals with acute pediatric secondary care services in North-West England. Children were recruited between November 2011 and May 2013 and were followed for 12 months. The protocol was approved by our local research ethics committee (NRES Committee North-West/Lancaster; research ethics committee approval number 11/NW/0262).

Study Participants

We screened children aged 3–17 years with physician-diagnosed asthma who had presented to the hospital with an asthma exacerbation. Children were excluded if already using allergen-impermeable bedding, if they had been born prematurely (<36 wk), or if they had another respiratory disease. Participants were skin prick tested once their exacerbation had resolved to evaluate for HDM, cat, dog, pollen, and other pet allergens if applicable (Stallergenes, Paris, France), and they were classed as sensitized if the wheal diameter was at least 3 mm greater than the negative control. Only children sensitized to HDM (with or without other allergens) were eligible for randomization. Parents provided written informed consent, and children provided assent.

Randomization and Masking

Children were randomly assigned 1:1 to active or placebo encasings by a researcher using a computer-based minimization procedure who was not otherwise involved in the study. Children were stratified for age (3–10 yr or 11–17 yr), household cigarette smoking, pet sensitization/ownership, and treatment level (Global Initiative for Asthma [GINA] steps 1–2 or step ⩾3; *see* Methods section in the online supplement) in a double-blind manner. To maintain blinding, no other information on HDM avoidance was given. All participants received identical printed washing instructions for the supplied encasings (*see* Methods section in the online supplement). The active encasings (Astex Pristine; ACP Solutions Ltd, Nailsworth, UK) were selected because their mite-proof efficacy had been demonstrated previously (20). Placebo encasings (made from a poly/cotton blend) were custom manufactured (Musbury Fabrics, Haslingden, UK) to match the active encasings (*see* Figure E1 in the online supplement). Neither encasing contained a

label. If more than one child from a family was allocated to the study, the second child was enrolled in the same arm as the index child to avoid potential unblinding. Researchers fitting covers and collecting dust samples for allergen analysis were not involved in follow-up.

Procedures

Children had their inhaler technique checked and corrected if necessary. Encasings were fitted to the pillow, mattress, and duvet of the child's bed. Other beds in the same room and beds in which participants spent more than one night per week were also encased.

Study Assessments

Baseline evaluation included questionnaires on demographics, past medical/family history, sleeping arrangements, pet exposure, and medication use. Interviewers masked to the child's group assignment conducted telephone interviews with the primary caregiver at 1, 4, 8, and 12 months to collect data on exacerbations, unscheduled medical care, and medication use. Quality of life (QOL) was assessed using the Pediatric Asthma Caregiver's Quality of Life Questionnaire (PACQLQ) (21), completed by parents; and the Mini PAQLQ (22), completed by children aged 7 years and older. Asthma control was assessed using the Asthma Control Questionnaire (ACQ) (23), completed for children aged 6 years or older.

Mite allergen (Der p 1) was measured in vacuumed dust samples collected from the child's mattress and lounge floor prior to fitting the encasings and at 12 months, using an enzyme-linked immunosorbent assay (INDOOR Biotechnologies, Cardiff, UK) (*see* Methods section in the online supplement).

Outcome Measures

The primary outcome was the occurrence of severe asthma exacerbations during the 12-month intervention period. We used the American Thoracic Society/European Respiratory Society definition of severe exacerbations (24), including the following:

1. A hospitalization or emergency department visit because of asthma, requiring systemic corticosteroids (OCSs), abbreviated to emergency hospital attendance
2. Use of OCSs, or an increase from a stable maintenance dose, for at least 3 days (including all OCS courses, regardless of whether associated with an emergency hospital attendance)

Secondary endpoints included change in controller treatment from baseline to 12 months, as well as PACQLQ (21), Mini PAQLQ (22), and ACQ (23) scores. Information on compliance with and acceptability of the intervention was recorded.

Statistical Methods

Power calculation. On the basis of data derived from the U.K. General Practice Research Database (now at www.cprd.com), we estimated that children who had at least one course of OCS in the previous 12 months had a mean exacerbation rate of 1.5/year (variance, 1.02). For 90% power to detect a 30% reduction in exacerbation rate during the 12-month intervention period,

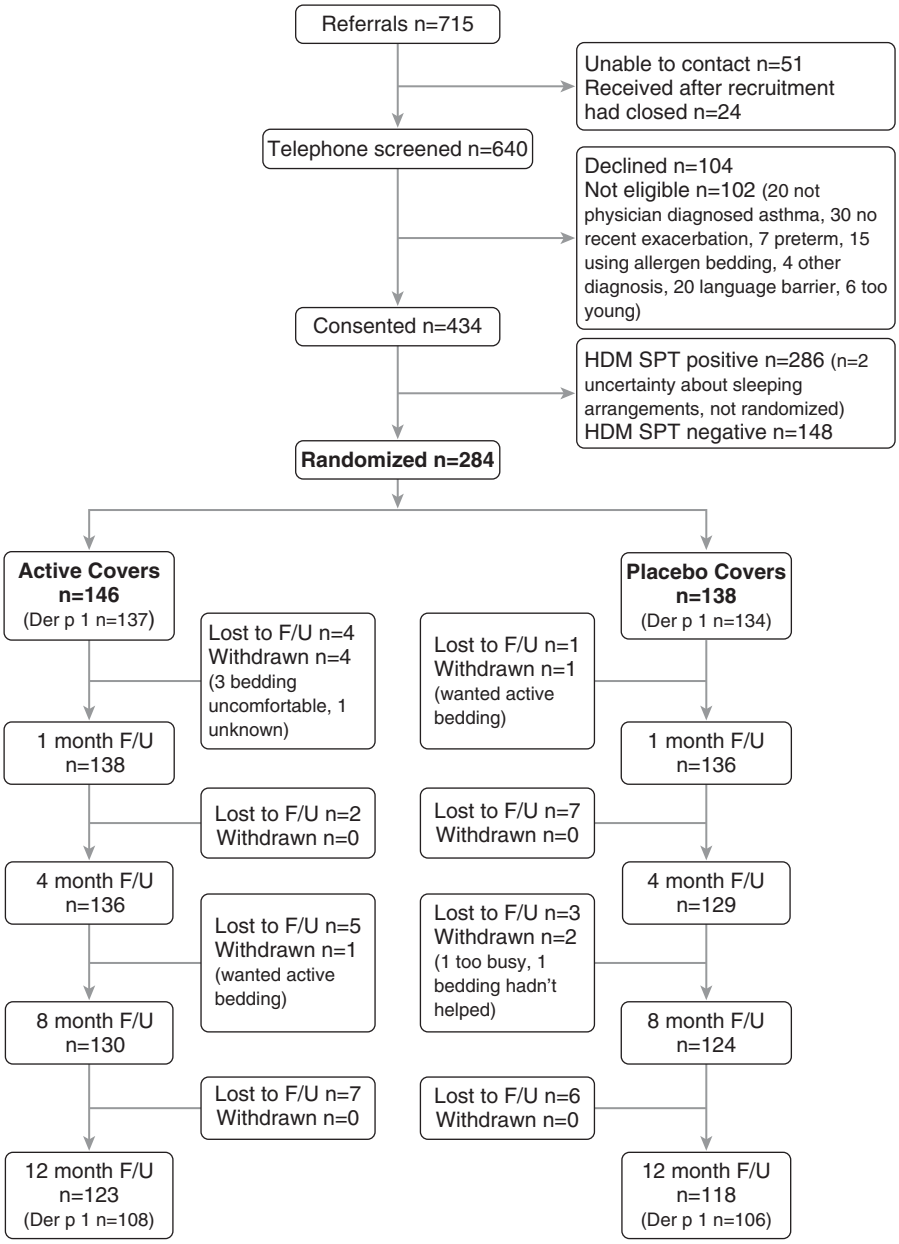


Figure 1. Consolidated Standards of Reporting Trials (CONSORT) flow diagram showing the participants' course during the study. Der p 1 = mite allergen; F/U = follow-up; HDM = house dust mite; SPT = skin prick testing.

114 children per group were required at a two-sided significance level of 0.05. Assuming 20% loss to follow-up, we aimed to randomize 284 children.

Data analysis. Baseline characteristics were compared between groups using *t* tests, the Mann-Whitney *U* test, and chi-square tests as appropriate. Efficacy analysis was performed according to the intention-to-treat principle (per-protocol analysis described in the online supplement). Outcomes were assessed between the groups using chi-square tests and logistic regression for children who completed 12 months of follow-up. Cox regression analysis was performed to assess time to first emergency hospital attendance and prednisolone use, and it included all evaluable data with censoring for those who did not complete 12 months of follow-up. Negative binomial generalized linear models were used to analyze count data for outcomes. Results are expressed as estimated marginal means (EMMs) and 95% confidence intervals (CIs) for annual rates/participant (25). Multivariable models were adjusted for age, sex, ethnic group, maintenance asthma treatment, hospitalizations in the 12 months prior to randomization, index of multiple deprivation, and tobacco smoke exposure. General linear models with repeated measures were used to compare mite allergen levels and prescribed treatments across time between the groups. Der p 1 levels were $\log_e$ transformed to normalize the data prior to analysis; results are presented as geometric means. The conventional two-sided 5% significance level was used.

Exploratory subgroup analyses (not prespecified) were conducted on the basis of age, GINA step, sensitization status, exposure to smoking, and socioeconomic status (*see* METHODS section in the online supplement) (26). Analyses were performed using IBM SPSS Statistics version 22 (IBM, Armonk, NY) and Stata 13 (StataCorp, College Station, TX) software.

Results

Patients

From November 2011 to May 2013, 434 children were screened to take part in the study. Of those, 286 were HDM sensitized, and 284 underwent randomization (146 to the active group and 138 to the placebo group) (Figure 1). Baseline characteristics

Table 1. Characteristics of Study Participants at Randomization

	Placebo Bedcovers (*n* = *138*)	Mite-Impermeable Bedcovers (Active) (*n* = *146*)	*P* Value
Age, yr, mean (SD)	7.45 (3.55)	7.11 (3.49)	0.42
Ages 3–10 yr	106 (76.8%)	117 (80.1%)	0.50
Ages 11–17 yr	32 (23.2%)	29 (19.9%)	
Male sex	94 (68.1%)	93 (63.7%)	0.43
Race/ethnicity		(n = 143)	0.96
White	89 (64.5%)	91 (63.6%)	
Asian	35 (25.4%)	36 (25.2%)	
Other	14 (10.1%)	16 (11.2%)	
Current hay fever	41 of 134 (30.6%)	46 of 129 (35.7%)	0.38
Current eczema	71 (51.8%)	57 of 140 (40.7%)	0.07
Food allergy	26 of 130 (20.0%)	40 of 138 (29.0%)	0.09
Maternal asthma	43 (31.2%)	39 of 142 (27.5%)	0.50
Paternal asthma	30 of 134 (22.4%)	40 of 142 (28.2%)	0.27
Maternal smoking	35 (25.4%)	34 of 145 (23.4%)	0.71
Paternal smoking	31 of 133 (23.3%)	43 of 141 (30.5%)	0.18
Smoking by a household member	57 (41.3%)	67 (45.9%)	0.44
Deprivation index, mean (SD)	34.16 (19.34)	34.74 (17.32)	0.79
Sensitized to*			
Mite	138 of 138 (100%)	146 of 146 (100%)	
Mite only	50 of 125 (40%)	60 of 130 (46.1%)	0.28
Cat	46 of 125 (36.8%)	46 of 130 (35.4%)	0.81
Dog	45 of 125 (36.0%)	44 of 130 (33.8%)	0.72
Grass	49 of 129 (38.0%)	46 of 136 (33.8%)	0.48
Aspergillus	8 of 126 (6.3%)	3 of 136 (2.2%)	0.09
Tree pollen	7 of 125 (5.6%)	4 of 135 (3.0%)	0.29
Number of allergens sensitized to, excluding HDM, median (IQR)	1 (0–2) (n = 131)	1 (0–2) (n = 135)	0.55
Pet contact	58 of 137 (42.3%)	64 of 145 (44.1%)	0.76
Cat owner	22 of 137 (16.1%)	21 of 145 (14.5%)	0.71
Dog owner	31 of 137 (22.6%)	36 of 145 (24.8%)	0.66
Sensitized and exposed to pet†	29 (21.0%)	31 (21.2%)	0.96
GINA step			0.98
GINA steps 1–2	72 (52.2%)	76 (52.1%)	
GINA step ⩾3	66 (47.8%)	70 (47.9%)	

Definition of abbreviations: GINA = Global Initiative for Asthma; HDM = house dust mite; IQR = interquartile range.
*All children had positive skin test results to house dust mite, but not all children completed the skin test for other allergens.
†Ascertained on the basis of skin prick testing or symptom reports from parents and pet ownership/exposure.

and Der p 1 levels were similar in both groups (Tables 1, E1, and E2). Twelve-month follow-up was completed for 123 (84.2%) in the active arm and 118 (85.5%) in the placebo arm; overall, 208 children (73.2%) reported full compliance throughout the study (per-protocol analysis).

Primary Outcomes

Hospitalization or emergency department visit because of asthma requiring systemic corticosteroids. Significantly fewer children in the active group than in the placebo group attended the hospital with one or more severe asthma exacerbations (36 of 123 [29.3%] vs. 49 of 118 [41.5%]; odds ratio, 0.58; 95% CI, 0.34–0.99; $P = 0.047$) (Figure 2A). Compared with the placebo group, time to first exacerbation requiring emergency hospital attendance was significantly longer in the active group ($P = 0.041$), and the risk of emergency hospital attendance was 45% lower in the active group (hazard ratio [HR], 0.55; 95% CI, 0.36–0.85; $P = 0.006$) (Figure 3; Table E3, multivariable model, adjusted for age, sex, GINA step, ethnicity, deprivation score, and tobacco smoke exposure). Although the annual rate of emergency hospital attendance was 27% lower in the active group than in the placebo group, this did not reach significance (EMM [95% CI], active, 0.38 [0.26–0.56]; vs. placebo, 0.52 [0.35–0.76]; $P = 0.18$). The distribution of the number of attendances did not differ between the groups ($P = 0.5$) (Figure E2).

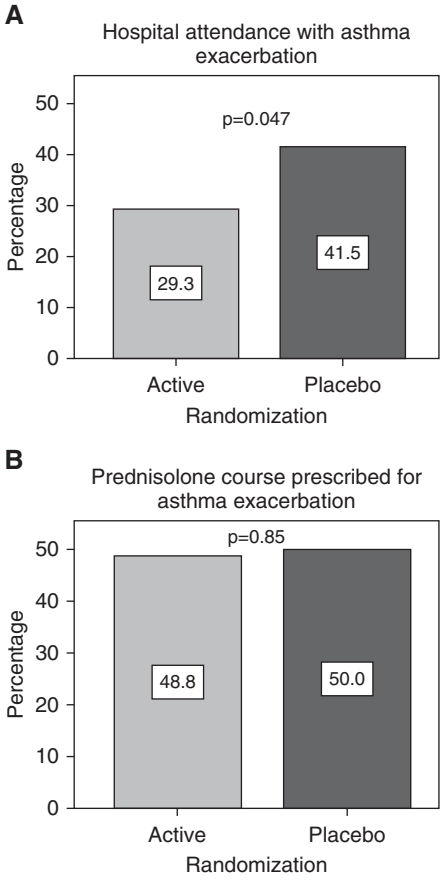


Figure 2. Percentage of children who experienced one or more severe exacerbations during the 12-month follow-up period (for all children who completed 12 months of follow-up; n = 241). Results are shown for (*A*) one or more hospitalizations or emergency department visits requiring systemic corticosteroids because of an asthma exacerbation ($P = 0.047$) and (*B*) the use of systemic corticosteroids for at least 3 days because of an asthma exacerbation ($P = 0.85$).

The per-protocol analysis is presented in the online supplement (Figures E3–E6). The risk of emergency hospital attendance was 54% lower in the active group than in the placebo group (HR, 0.46; 95% CI, 0.28–0.76; $P = 0.002$).

Use of oral corticosteroids for 3 days or longer. There was no difference in the number of children who received a course of OCS for an asthma exacerbation (whether associated with an unscheduled hospital or general practitioner attendance or a home rescue pack) between the groups (active, 48.8%; vs. placebo, 50.0%; $P = 0.85$) (Figure 2B). In investigating the time to first OCS use, we found that there was no difference between groups in the univariable analysis ($P = 0.67$) or in the multivariable model (HR, 0.82; 95% CI, 0.58–1.17; $P = 0.28$). The annual rate of OCS courses prescribed was not different between the groups (EMM [95% CI], active, 0.77 [0.55–1.06]; vs. placebo, 0.85 [0.62–1.16]; $P = 0.57$). Per-protocol analysis is presented in the online supplement (Figure E3B).

Secondary Outcomes

Mean values for PACQLQ and ACQ at each time point are presented in Table E4. Parents of children in both groups reported significantly improved PACQLQ between 1 and 12 months (mean difference [95% CI], active, 0.50 points [0.14–0.8]; $P = 0.007$; placebo, 0.57 points [0.12–1.02]; $P = 0.01$), with no difference between the groups. Although significant improvement in ACQ score over time was observed only in children in the active group (−0.56 points [−0.18, −0.93]; $P = 0.004$), and not in those with placebo bedcovers (−0.25 points [−0.61, 0.11]; $P = 0.16$), there was no difference between the groups.

There was no difference in GINA steps between the two groups at baseline (Tables 1 and E1). At the end of the intervention period, GINA step had been increased in 10.7% of the active group and in 14.5% of the placebo group ($P = 0.37$). Children who had any exacerbations during follow-up were more likely to have their GINA step increased by the end of follow-up compared with children who did not experience an exacerbation (27.1% vs. 4.5%, respectively; $P < 0.001$), regardless of group allocation.

Children in the active group were more likely to complain about the encasings (Table E5). Despite this, the number adhering to the intervention at 12 months was similar in both groups (101 in the active group and 107 in the placebo group; $P = 0.11$). Among all those fully compliant with the bedding, almost 90% reported that they would continue to use the encasings after the study.

Mite Allergen Levels

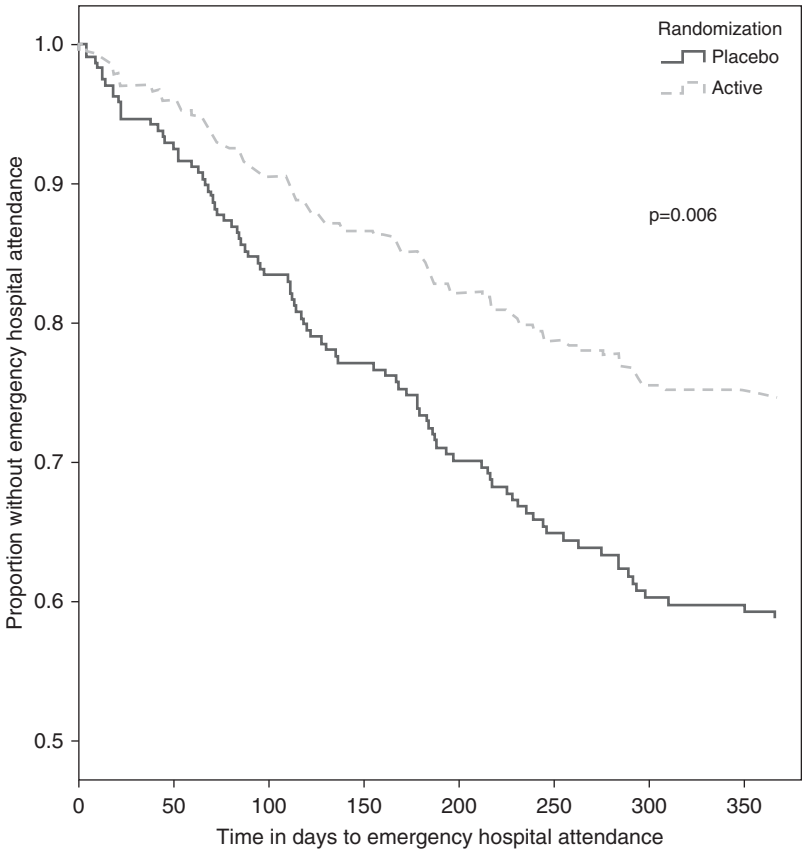
Der p 1 levels in dust from the children's mattresses was reduced by 84% in the active group after the intervention, with no change in the placebo group ($P < 0.001$) (Figure 4). Der p 1 in the lounge floor was unchanged in both groups ($P = 0.48$) (Figure E7).

Post Hoc Analyses

In a multivariable Cox regression analysis (Table E6), a reduction in risk of emergency hospital attendance was seen for children in the active group aged 3–10 years (HR, 0.54; 95% CI, 0.33–0.87; $P = 0.01$) (Figure E8), in those sensitized only to mite ($P = 0.04$), in those from homes without smokers ($P = 0.02$), in those on GINA treatment step 3 or higher ($P = 0.03$), and in those from the most deprived homes ($P = 0.01$). None of the interaction terms were significant, however. Also, in younger children (aged 3–10 yr), a nonsignificant reduction in risk of OCS use was seen in those in the active group (HR, 0.69; 95% CI, 0.46–1.04; $P = 0.08$) (Figure E9).

Discussion

In our study of children with HDM allergy who had recently experienced a severe



Number at risk

Placebo	136	119	105	94	89	77	71	70
Active	136	129	121	112	102	91	88	88

Figure 3. Time to first hospitalization or emergency department visit because of severe exacerbation of asthma. The model was adjusted for age, sex, ethnic group, maintenance asthma treatment, number of hospitalizations in the 12-month period prior to randomization, index of multiple deprivation, and tobacco smoke exposure. The risk was 45% lower in the active group than in the placebo group ($P = 0.006$).

asthma exacerbation, the risk of further severe asthma exacerbations requiring emergency hospital attendance was reduced by 45% in those who had mite-impermeable encasings fitted to the mattress, pillow, and duvet. To our knowledge, this is the first study of the effect of such an intervention on exacerbations in children. The annual rate of emergency hospital attendance, though 27% lower in the active group than in the placebo group, was not significantly reduced ($P = 0.18$). There was no difference in the proportion of children requiring courses of oral steroids for asthma exacerbations. The encasings were highly effective in reducing recoverable mite allergen.

Asthma exacerbations have been ranked highly by clinicians and parents as important outcomes for clinical trials in children (27). Although comparatively rare events, severe asthma exacerbations result in many hospital admissions, which are particularly costly, emphasizing the relevance of this as an outcome. Using real data derived from the U.K. General Practice Research Database to power the study, we estimated that the exacerbation rate would be 1.5/year for children who had experienced an exacerbation in the previous year. As previous hospitalizations/exacerbations are among the best predictors of future risk (3, 28), we recruited children when attending the hospital with an exacerbation. However, our observed exacerbation rate during follow-up was materially lower (placebo group, 0.85 OCS courses/yr), reducing our power to detect significant differences between the groups. That we were able to detect a statistically significant difference between groups for the number of children requiring hospital attendance for asthma exacerbations reflects the large effect size seen.

Although the number of children who experienced any emergency hospital attendance with an asthma exacerbation was significantly reduced after the active intervention, some children continued to have hospital attendance, and a few of them had multiple attendances. However, the distribution of multiple attendances did not differ between treatment groups.

As with many treatments for asthma (e.g., long-acting β-agonists, leukotriene receptor antagonists), it is clear that some individuals respond to the treatment and others do not (29), but predicting those who will respond is challenging. Although our trial was not powered to carry out subgroup analyses, we performed exploratory analyses in an attempt to identify the characteristics of the children who showed the best response. This indicated that younger children, those sensitized only to mite, those with more severe disease (GINA step 3+), and those not exposed to smoking had fewer emergency hospital attendances. Similar subgroup analyses in those requiring OCS courses for asthma exacerbations also suggested that younger children may be more likely to respond to this intervention. While recognizing that the subgroup analysis is exploratory, we propose that allergen avoidance may be more effective in younger children, in whom the disease may have been present for a shorter time. This may be analogous to occupational asthma, where removal of allergen exposure is effective if done soon after the onset of disease (30), and it may explain the differences between our results and those of large studies in adults (31). In addition, younger children may spend a higher proportion of time in bed, making this dust reservoir a potentially larger contributor to personal mite exposure than in older children or adults. Recent reports regarding adults suggested that mite exposure may be higher during the daytime and may reflect lifestyle as well as clothing worn (32). We speculate that personal allergen exposure is different in young children, who generally wear clothes that can be hot washed and undertake different activities. We have no evidence that the younger children were more compliant with the intervention.

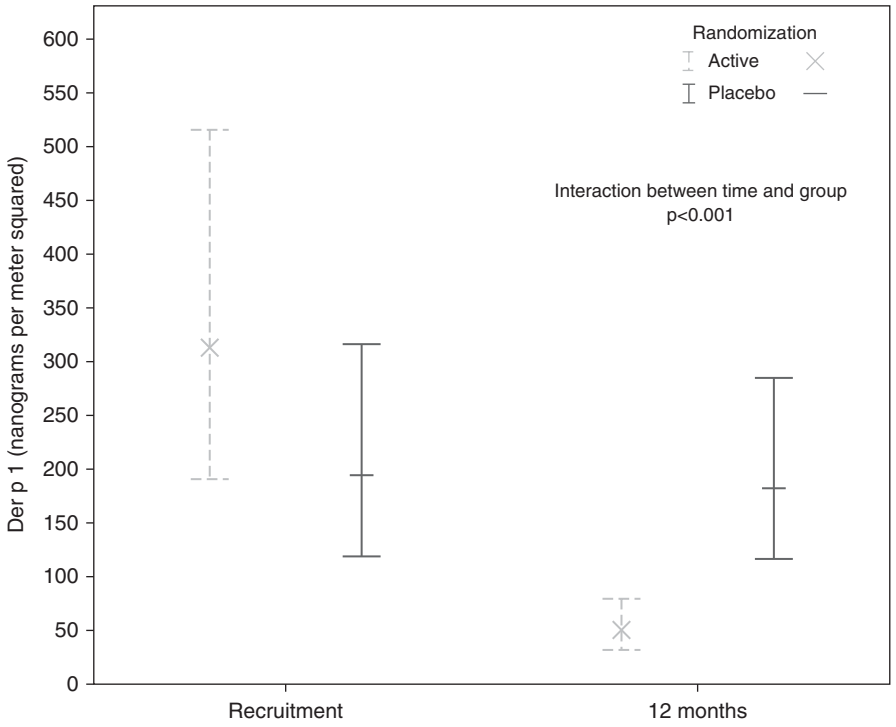


Figure 4. Mite allergen (Der p 1) levels in child's mattress (ng/m^2) at recruitment and 12 months after intervention. Results are shown as geometric mean and 95% confidence intervals for active (mite-impermeable) bedcovers (*dashed line*) and placebo bedcovers (*solid line*).

Despite the risk of emergency hospital attendance being reduced in the active group, the risk of receiving OCSs was not significantly reduced, although a trend was seen in younger children. A few OCS courses were administered by parents using home rescue packs without contemporaneous medical direction (eight 3-day courses in six children in total), some of which may have been unnecessary. Unfortunately, we were unable to assess children to confirm the presence of an exacerbation; care was provided by their family doctor or by urgent care services as the parents saw appropriate. It may be that the study intervention genuinely reduced the severity of exacerbations, resulting in fewer hospital attendances but not fewer courses of OCSs.

Many factors influence consulting behaviors in parents with sick children; our recruitment strategy may have selected those more likely to present to the hospital. Indeed, in our population, the majority of exacerbations resulted in an emergency hospital attendance (∼70%). It is likely, however, that those exacerbations requiring an emergency hospital attendance were more severe, and regardless of that, they are certainly more expensive to the provider, so we believe that the reduction seen is of clinical importance.

To establish that the reduction in exacerbations seen was not due to changes in controller medication, we examined changes in prescribed medication during follow-up and found no difference between the groups. All treatments were prescribed by the participants' usual physicians, who were blinded to the treatment allocation and not influenced by the study team.

Because there is no QOL score for patients with asthma or caregivers validated for use in children younger than 7 years of age, we used the PACQLQ for all participants (recognizing that this has limitations) and the Mini PAQLQ for children older than 7 years of age. There were no between-group differences in QOL (both tending to show within-group improvements). Interestingly, despite recent exacerbations, both groups reported good QOL and control at baseline, leaving little prospect of demonstrating significant between-group differences.

Children who were in the active group complained more about the bedding than those using the placebo bedcovers. It is possible that this difference in perception led to unblinding of individuals (i.e., believing that they must have the real bedcovers because they are uncomfortable). However, we believe this is unlikely to have affected the results of the study, given the objective nature of our outcomes. It is important to note that compliance with the bedcovers was not significantly different between the groups, and adherence (>70%) appeared to be at least as good as, if not better than, with medications usually prescribed for asthma (e.g., inhaled corticosteroids, ∼50%) (33).

There are some other limitations to our study. All data on exacerbations and OCS use were reported by parents/carers and not confirmed by their primary care physicians. However, we gathered information from parents on a 3-monthly basis; therefore, recall should not be a significant issue, and we would expect any bias to be similar across the groups. We were unable to measure adherence to prescribed treatment within this study, and although it is unlikely that one arm was more adherent than the other, we cannot exclude this from having occurred. Evidence derived from previous studies suggests that viruses and allergens in sensitized individuals act synergistically to increase the risk of asthma exacerbation and hospitalization. Because we have no information on the trigger for individual exacerbations (viral or otherwise), we were unable to perform an analysis to identify whether the effectiveness of the intervention was dependent upon the trigger.

Conclusions

We found that the simple and relatively cheap intervention of mite allergen–impermeable bed encasings, costing around £130/US$200, is effective in reducing emergency hospital attendance with severe asthma exacerbations. In the population we studied, we estimate that approximately eight children would need to be treated to prevent one child having any hospital attendance in the following year. It is likely that there is a subgroup of children in whom the intervention is more beneficial, and although our subgroup analysis would suggest this group might represent younger, monosensitized children in nonsmoking households, further research is required to clarify this. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Acknowledgment: The authors thank the children and their parents for their participation. The authors also thank Anna Duxbury for her assistance with recruitment and data collection and Mandy Mycock for the dust sample collection (both of whom received salaries from the grant). The authors greatly appreciate Sarah Rickard and the team from the National Institute for Health Research (NIHR) Greater Manchester, Lancashire and Cumbria Medicines for Children Research Network, who assisted with recruitment across the region. In addition, the authors thank Lesley Oldham for assistance with the database and its management. The authors also thank Dr. Simon Stephan and the NIHR South Manchester Respiratory and Allergy Clinical Research Facility for assistance with laboratory work. The authors thank Hazera Begum for collecting user feedback. The authors also thank the PAXAMA principal investigators: Dr. Shirley Castille, Dr. Chris Cooper, Dr. Sharryn Gardner, Dr. Susan Glass, Dr. Kate Goldberg, Dr. Prakash Kamath, Amy Lamb, Dr. David Levy, Dr. Naveen Rao, Dr. Tanya Robertson, and Dr. Karnam Sugumar. None of these individuals received additional funding for their contributions.

References

1. Hasegawa K, Bittner JC, Nonas SA, Stoll SJ, Watase T, Gabriel S, Herrera V, Camargo CA Jr; Multicenter Airway Research Collaboration-37 Investigators. Children and adults with frequent hospitalizations for asthma exacerbation, 2012–2013: a multicenter observational study. *J Allergy Clin Immunol Pract* 2015;3: 751–758.e1.
2. Lane S, Molina J, Plusa T. An international observational prospective study to determine the cost of asthma exacerbations (COAX). *Respir Med* 2006;100:434–450.
3. Schatz M, Cook EF, Joshua A, Petitti D. Risk factors for asthma hospitalizations in a managed care organization: development of a clinical prediction rule. *Am J Manag Care* 2003;9: 538–547.
4. Johnston SL, Pattemore PK, Sanderson G, Smith S, Lampe F, Josephs L, Symington P, O'Toole S, Myint SH, Tyrrell DA, *et al*. Community study of role of viral infections in exacerbations of asthma in 9-11 year old children. *BMJ* 1995;310:1225–1229.
5. Heymann PW, Platts-Mills TA, Johnston SL. Role of viral infections, atopy and antiviral immunity in the etiology of wheezing exacerbations among children and young adults. *Pediatr Infect Dis J* 2005;24(11 Suppl):S217–S222.
6. Cox DW, Bizzintino J, Ferrari G, Khoo SK, Zhang G, Whelan S, Lee WM, Bochkov YA, Geelhoed GC, Goldblatt J, *et al*. Human rhinovirus species C infection in young children with acute wheeze is associated with increased acute respiratory hospital admissions. *Am J Respir Crit Care Med* 2013;188:1358–1364.
7. Murray CS, Poletti G, Kebadze T, Morris J, Woodcock A, Johnston SL, Custovic A. Study of modifiable risk factors for asthma exacerbations: virus infection and allergen exposure increase the risk of asthma hospital admissions in children. *Thorax* 2006;61: 376–382.
8. Soto-Quiros M, Avila L, Platts-Mills TA, Hunt JF, Erdman DD, Carper H, Murphy DD, Odio S, James HR, Patrie JT, *et al*. High titers of IgE antibody to dust mite allergen and risk for wheezing among asthmatic children infected with rhinovirus. *J Allergy Clin Immunol* 2012;129: 1499–1505.e5.
9. Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention: 2015 [accessed 2015 Jul 7]. Available from: http://ginasthma.org/wp-content/uploads/2016/01/GINA_Pocket_2015.pdf
10. National Institute for Health and Care Excellence (NICE). Omalizumab for treating severe persistent allergic asthma: technology appraisal guidance [TA278]. NICE; 2013 [created 2013 Apr 24; accessed 2015 Jul 7]. Available from: https://www.nice.org.uk/guidance/TA278
11. Custovic A, Simpson A. The role of inhalant allergens in allergic airways disease. *J Investig Allergol Clin Immunol* 2012;22: 393–401.
12. Gøtzsche PC, Johansen HK. House dust mite control measures for asthma. *Cochrane Database Syst Rev* 2008;2:CD001187.
13. Carswell F, Birmingham K, Oliver J, Crewes A, Weeks J. The respiratory effects of reduction of mite allergen in the bedrooms of asthmatic children—a double-blind controlled trial. *Clin Exp Allergy* 1996;26: 386–396.
14. Carter MC, Perzanowski MS, Raymond A, Platts-Mills TA. Home intervention in the treatment of asthma among inner-city children. *J Allergy Clin Immunol* 2001;108:732–737.
15. Halken S, Høst A, Niklassen U, Hansen LG, Nielsen F, Pedersen S, Osterballe O, Veggerby C, Poulsen LK. Effect of mattress and pillow encasings on children with asthma and house dust mite allergy. *J Allergy Clin Immunol* 2003;111:169–176.
16. Morgan WJ, Crain EF, Gruchalla RS, O'Connor GT, Kattan M, Evans R III, Stout J, Malindzak G, Smartt E, Plaut M, *et al*.; Inner-City Asthma Study Group. Results of a home-based environmental intervention among urban children with asthma. *N Engl J Med* 2004;351: 1068–1080.
17. Shapiro GG, Wighton TG, Chinn T, Zuckrman J, Eliassen AH, Picciano JF, Platts-Mills TA. House dust mite avoidance for children with asthma in homes of low-income families. *J Allergy Clin Immunol* 1999;103: 1069–1074.
18. Green RM, Custovic A, Sanderson G, Hunter J, Johnston SL, Woodcock A. Synergism between allergens and viruses and risk of hospital admission with asthma: case-control study. *BMJ* 2002;324:763. [Published erratum appears in *BMJ* 2002; 324:1131.]
19. Murray CS, Sumner H, Mycock M, Duxbury A, Custovic A, Simpson A. Preventing asthma exacerbations by allergen-impermeable bed covers in children: double-blind randomised placebo controlled trial [abstract 151]. *Allergy* 2015;70(Suppl 101):75.
20. Vaughan JW, McLaughlin TE, Perzanowski MS, Platts-Mills TA. Evaluation of materials used for bedding encasement: effect of pore size in blocking cat and dust mite allergen. *J Allergy Clin Immunol* 1999;103:227–231.
21. Juniper EF, Guyatt GH, Feeny DH, Ferrie PJ, Griffith LE, Townsend M. Measuring quality of life in the parents of children with asthma. *Qual Life Res* 1996;5:27–34.
22. Juniper EF, Guyatt GH, Feeny DH, Ferrie PJ, Griffith LE, Townsend M. Measuring quality of life in children with asthma. *Qual Life Res* 1996; 5:35–46.
23. Juniper EF, Gruffydd-Jones K, Ward S, Svensson K. Asthma Control Questionnaire in children: validation, measurement properties, interpretation. *Eur Respir J* 2010;36:1410–1416.
24. Reddel HK, Taylor DR, Bateman ED, Boulet LP, Boushey HA, Busse WW, Casale TB, Chanez P, Enright PL, Gibson PG, *et al*.; American Thoracic Society/European Respiratory Society Task Force on Asthma Control and Exacerbations. An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. *Am J Respir Crit Care Med* 2009; 180:59–99.
25. Fuhlbrigge A, Peden D, Apter AJ, Boushey HA, Camargo CA Jr, Gern J, Heymann PW, Martinez FD, Mauger D, Teague WG, *et al*. Asthma outcomes: exacerbations. *J Allergy Clin Immunol* 2012;129(3 Suppl): S34–S48.
26. Wang R, Lagakos SW, Ware JH, Hunter DJ, Drazen JM. Statistics in medicine: reporting of subgroup analyses in clinical trials. *N Engl J Med* 2007;357:2189–2194.
27. Sinha IP, Gallagher R, Williamson PR, Smyth RL. Development of a core outcome set for clinical trials in childhood asthma: a survey of clinicians, parents, and young people. *Trials* 2012;13: 103.
28. Pollack CV Jr, Pollack ES, Baren JM, Smith SR, Woodruff PG, Clark S, Camargo CA; Multicenter Airway Research Collaboration Investigators. A prospective multicenter study of patient factors associated with hospital admission from the emergency department among children with acute asthma. *Arch Pediatr Adolesc Med* 2002; 156:934–940.

29. Lemanske RF Jr, Mauger DT, Sorkness CA, Jackson DJ, Boehmer SJ, Martinez FD, Strunk RC, Szefler SJ, Zeiger RS, Bacharier LB, *et al*.; Childhood Asthma Research and Education (CARE) Network of the National Heart, Lung, and Blood Institute. Step-up therapy for children with uncontrolled asthma receiving inhaled corticosteroids. *N Engl J Med* 2010; 362:975–985.
30. Dykewicz MS. Occupational asthma: current concepts in pathogenesis, diagnosis, and management. *J Allergy Clin Immunol* 2009;123:519–528, quiz 529–530.
31. Woodcock A, Forster L, Matthews E, Martin J, Letley L, Vickers M, Britton J, Strachan D, Howarth P, Altmann D, *et al*.; Medical Research Council General Practice Research Framework. Control of exposure to mite allergen and allergen-impermeable bed covers for adults with asthma. *N Engl J Med* 2003;349:225–236.
32. Tovey ER, Willenborg CM, Crisafulli DA, Rimmer J, Marks GB. Most personal exposure to house dust mite aeroallergen occurs during the day. *PLoS One* 2013;8:e69900.
33. Morton RW, Everard ML, Elphick HE. Adherence in childhood asthma: the elephant in the room. *Arch Dis Child* 2014;99:949–953.