Preventing Severe Asthma Exacerbations in Children

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Preventing exacerbations by avoiding mite allergen

Preventing severe asthma exacerbations in children: A randomised trial of mite impermeable bedcovers

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AUTHOR CONTRIBUTIONS

Clare Murray and Angela Simpson had 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.

Study concept and design: Clare Murray, Angela Simpson, Adnan Custovic

Acquisition, analysis, or interpretation of data: Clare Murray, Angela Simpson, Adnan Custovic, Helen Sumner, Phil Foden, Elizabeth Shepley

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Critical revision of the manuscript for important intellectual content: Clare Murray, Angela Simpson, Adnan Custovic, Helen Sumner, Phil Foden, Elizabeth Shepley

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Study supervision: Clare Murray, Angela Simpson

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At a glance commentary

Scientific knowledge on the Subject: Asthma exacerbations in children are a leading cause of hospitalisation. Exposure in sensitised individuals in synergy with viral infections greatly increases hospital admission risk. In the developed world house dust mite is the commonest sensitising allergen. Studies to date have not 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 in mite sensitised asthmatic children can significantly reduce the risk of severe exacerbations resulting in emergency hospital attendance.

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

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ABSTRACT

Rationale: Allergen exposure in sensitised asthmatics interacts with viruses in increasing the risk of asthma exacerbation.

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

Methods: We randomized mite-sensitised asthmatic children (3-17 years), following an emergency hospital attendance with an asthma exacerbation, to receive mite-impermeable (Active) or control (Placebo) bed encasings.

Measurements and main results: Over a 12-month intervention period the occurrence of severe asthma exacerbations were investigated. Of 434 asthmatic children who consented, 286 (mean age 7.7 years, 65.8% male) were mite sensitised and 284 were randomised (146 Active; 138 Placebo). At 12 months, significantly fewer children in the Active group had attended hospital with an exacerbation compared to the Placebo group (36/123 [29.3%] versus 49/118 [41.5%], $p=0.047$). In the multivariable analysis, the risk of emergency hospital attendance was 45% lower in the Active group (Hazard Ratio 0.55 [95%CI, 0.36-0.85], $p=0.006$) compared with the Placebo group. The annual rate of emergency hospital attendance with exacerbations was 27% lower in the Active compared with 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 [0.58-1.17], $p=0.28$).

Conclusions: Mite-impermeable encasings are effective in reducing the number of mite sensitised asthmatic children attending hospital with asthma exacerbations, but not the

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number requiring oral prednisolone. This simple measure may reduce the health care burden of asthma exacerbations in children.

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Key words: Asthma, Exacerbations, Allergens, Dermatophagoides, Avoidance, Child

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INTRODUCTION

Asthma is the most common chronic disease in childhood. Although most children with asthma are well-controlled on pharmacotherapies, a significant number experience exacerbations which remain one of the commonest reasons for paediatric 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 3-fold (2). Previous hospital admissions predict future hospitalizations (3). Respiratory virus infections are major risk factors for hospital admission (4-6), particularly amongst children who are exposed to allergens to which they are sensitised, where these factors act synergistically to markedly increase the risk of hospital admission (7, 8). However, disrupting this interaction in atopic asthmatics is challenging. There are currently no available vaccines for viruses which 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, no studies to date have investigated the effect of allergen avoidance on asthma exacerbations and hospital admissions, instead focussing on symptom scores, medication usage and lung function.

House dust mite (HDM) is a common allergen linked to expression of asthma, with ~65% of UK asthmatic children demonstrating sensitisation (7). Although high HDM exposure has been linked to asthma severity (11), a meta-analysis of 44 trials of mite avoidance was unable to demonstrate any clinical benefit of measures designed to reduce mite exposure, and concluded

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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 did not distinguish between adult and paediatric studies. Indeed, most studies which 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 which have poor access to healthcare/medications (14, 16). Given the evidence of a synergism between viral infection and allergen exposure in increasing the risk of asthma exacerbations in sensitised individuals (7, 18), we hypothesized that effective reduction in mite exposure may reduce the risk of exacerbations in these patients.

In this double-blind study, Preventing asthma exacerbations by avoiding mite allergen (PAXAMA), we compared the effect of mite-impermeable bed covers to that of placebo covers in reducing the risk of severe asthma exacerbations in mite-sensitised asthmatic children, who had recently attended hospital with an asthma exacerbation. Some of the results of these studies have been 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 bed covers on the risk of severe asthma exacerbations in mite-sensitised asthmatic children was conducted across 14 hospitals with acute pediatric secondary care services in North-West England. Children were recruited between November 2011 and May

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2013 and were followed for 12 months. The protocol was approved by local research ethics committee (NRES Committee North-West/Lancaster, REC approval number 11/ NW/0262).

STUDY PARTICIPANTS

We screened children aged 3-17 years with physician-diagnosed asthma who had presented to hospital with an asthma exacerbation. Children were excluded if already using allergen-impermeable bedding, born prematurely (<36 weeks) or had another respiratory disease. Participants were skin-prick tested once their exacerbation had resolved, to HDM, cat, dog, pollen and other pet allergens if applicable (Stallergenes, Paris, France), and classed as sensitized if the weal diameter was at least 3mm greater than the negative control. Only children sensitised to HDM (+/- other allergens) were eligible for randomisation. Parents provided written informed consent and children assent.

Randomisation and Masking

Children were randomly assigned 1:1 to active or placebo encasings using a computer-based minimisation procedure by a researcher who was not otherwise involved in the study. Children were stratified for age (3-10 years; 11-17 years), household cigarette smoking, pet sensitisation/ownership and treatment level (GINA steps 1-2; ≥ 3 ; eMethods, 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 (eMethods, Online Supplement). The active encasings (Astex Pristine, ACP solutions Ltd, Gloucestershire, UK) were selected because their mite-proof efficacy had been demonstrated previously (20). Placebo encasings (made from poly-cotton) were custom manufactured (Musbury Fabrics, Rossendale, UK), to match the active encasings (Figure E1).

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Neither encasings contained a label. If more than one child from a family were 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 >1 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 one, four, eight and twelve months to collect data on exacerbations, unscheduled medical care and medication. Quality of life (QOL) was assessed using Pediatric Asthma Caregiver's Quality of Life Questionnaire PACQLQ(21) completed by parents, mini Pediatric Asthma Quality of Life Questionnaire (PAQLQ)(22) completed by children age ≥ 7 years, and asthma control by Asthma Control Questionnaire (ACQ)(23) completed in children aged 6 years or over.

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 enzyme-linked immunosorbent assay (Indoor Biotechnologies, Cardiff, UK; eMethods, Online Supplement)

OUTCOME MEASURES

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The primary outcome was the occurrence of severe asthma exacerbations during the 12-month intervention period. We used ATS/ERS definition of severe exacerbations (24), including:

(A) A hospitalization or emergency department (ED) visit because of asthma, requiring systemic corticosteroids (OCS) – abbreviated to emergency hospital attendance;

(B) Use of OCS or an increase from a stable maintenance dose, for ≥ 3 days (includes all OCS courses whether associated with an emergency hospital attendance or not).

Secondary endpoints included change in controller treatment from baseline to 12 months, PACQLQ(21), mini PAQLQ(22) and ACQ(23) scores. Compliance and acceptability of intervention was recorded.

STATISTICAL METHODS

Power calculation

Data from UK General Practice Research Database (GPRD; www.gprd.com) estimated that children who had ≥ 1 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, 114 children per group were required, at a two-sided significance level of 0.05. Assuming 20% lost during follow-up, we aimed to randomise 284 children.

Data Analysis

Baseline characteristics were compared between groups using t-tests, Mann-Whitney U and chi-squared tests as appropriate. Efficacy analysis was performed according to the intention-to-treat principle (per-protocol analysis in supplement). Outcomes were assessed between the groups using chi-squared tests and logistic regression for children who completed 12 months of

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follow-up. Cox regression analysis assessed time to first emergency hospital attendance and prednisolone usage, and included all evaluable data with censoring for those who did not complete 12 months follow-up. Negative binomial generalized linear models analysed count data for outcomes; results expressed as estimated marginal means (EMM) and 95% confidence intervals (CI) for annual rates/participant (25). Multivariable models were adjusted for age, gender, ethnic group, maintenance asthma treatment, hospitalisations in the 12-months prior to randomisation, 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 normalise the data prior to analysis; results presented as geometric means (GM). The conventional two-sided 5% significance level was used.

Exploratory subgroup analyses (not pre-specified) were conducted based on age, GINA step, sensitisation status, exposure to smoking and socioeconomic status (eMethods in Supplement) (26).

Analyses were carried out using SPSS 22 (IBM, New York, USA) and Stata 13 (StataCorp, Texas, USA).

RESULTS

PATIENTS

From November 2011 to May 2013, 434 children were screened to take part in the study. Of those, 286 were HDM-sensitised and 284 underwent randomization (146 Active; 138 Placebo; Figure 1). Baseline characteristics and Der p 1 levels were similar in both groups (Table 1;

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Tables E1, E2). Twelve month follow-up was completed in 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 outcome

A) Hospitalization or ED visit because of asthma requiring systemic corticosteroids

Significantly fewer children in the Active group attended hospital with one or more severe asthma exacerbations compared to the Placebo group (36/123 [29.3%] versus 49/118 [41.5%]; OR 0.58 (0.34, 0.99), $p=0.047$; Figure 2A).

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 [0.36-0.85], $p=0.006$), compared with the Placebo group (Figure 3; Table E3, multivariable model, adjusted for age, gender, GINA step, ethnicity, deprivation score and tobacco smoke exposure). Although, the annual rate of emergency hospital attendance was 27% lower in the Active compared with 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 numbers of attendances did not differ between the groups ($p=0.5$; Figure E2).

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 compared to the Placebo group (HR 0.46 [0.28-0.76]; $p=0.002$).

B) Use of oral corticosteroids for ≥ 3 days

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There was no difference in the numbers of children who received a course of OCS for an asthma exacerbation (whether associated with an unscheduled hospital or general practitioner attendance or by a home rescue pack) between the groups (Active 48.8% vs Placebo 50.0%, $p=0.85$, Figure 2B).

Investigating the time to first OCS use, there was no difference between groups in the univariable analysis ($p=0.67$) or in the multivariable model (HR 0.82 [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 are presented in Table E4 in the online supplement. Parents of children in both groups reported significantly improved PACQLQ between one 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 Active children (-0.56 points, [-0.18,-0.93], $p=0.004$), and not in those with Placebo covers (-0.25 points, [-0.61, 0.11], $p=0.16$), there was no difference between the groups.

There was no difference in GINA step between the two groups at baseline (Table1, Table E1). At the end of the intervention period, GINA step had been increased in 10.7% of the Active group and 14.5% of 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 to

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children who did not suffer an exacerbation (27.1% vs 4.5% respectively, $p<0.001$), irrespective 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 Active, 107 Placebo, $p=0.11$). Amongst all those fully compliant with the bedding almost 90% reported they would continue to use the encasings after the study.

MITE ALLERGEN LEVELS

Der p 1 levels in dust from the child's mattress was reduced by 84% in the Active group following 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 an emergency hospital attendance was seen for children in the Active group aged 3-10 years (HR 0.54 [0.33-0.87], $p=0.01$, Figure E8), in those sensitised only to mite ($p=0.04$), in those from non-smoking homes ($p=0.02$), in those on GINA treatment step ≥ 3 ($p=0.03$) and in those from the most deprived homes ($p=0.01$). None of the interaction terms were significant however. Also, in younger children (3-10years), a non-significant reduction in risk of OCS use was seen in those in the Active group (HR 0.69 [0.46-1.04], $p=0.08$, Figure E9).

DISCUSSION

In our study of HDM allergic children who had recently suffered a severe asthma exacerbation, the risk of further severe asthma exacerbations requiring an emergency hospital attendance

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was reduced by 45% in those who had mite-impermeable encasings fitted to the mattress, pillow and duvet. 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 compared to 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 (28). Using real data from UK GPRD to power the study, we estimated that the exacerbation rate would be 1.5/annum for children who had suffered an exacerbation in the previous year. As previous hospitalizations/exacerbations are amongst the best predictors of future risk (3,29), we recruited children when attending hospital with an exacerbation. However, our observed exacerbation rate during follow-up was materially lower (Placebo group: 0.85 oral corticosteroid courses/annum), reducing our power to detect significant differences between the groups. That we were able to detect a statistically significant difference between groups for numbers of children requiring hospital attendances 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 following the active intervention, some children continued to have hospital attendances, a few of them having multiple attendances. However, the distribution of multiple attendances did not differ between treatment groups.

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As with many treatments for asthma (e.g. long acting Beta-agonists, leukotriene receptor antagonists), it is clear that some individuals respond to the treatment and others do not (30), 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 sensitised only to mite, those with more severe disease (GINA 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. Whilst recognising 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 (31), and may explain the differences between our results compared to large studies in adults (32). 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 in adults suggested that mite exposure may be higher during the daytime, and may reflect lifestyle and clothing worn (33). 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.

Despite the risk of emergency hospital attendance being reduced in the Active group, the risk of receiving OCS was not significantly reduced, although a trend was seen in younger children. A

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small number of OCS courses were administered by parents using home rescue packs without contemporaneous medical direction (eight, three day courses, in total in 6 children), 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 OCS.

Many factors influence consulting behaviours in parents with sick children; our recruitment strategy may have selected those more likely to present to 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 are certainly more expensive to the provider, and so we believe that the reduction seen is of clinical importance.

In order 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 blind to the treatment allocation and not influenced by the study team.

As there is no QOL score for asthma sufferers or caregivers validated for use in children under seven years, we used the PACQLQ for all participants (recognising that this has limitations), and the mini PAQLQ for children over seven years. There were no between-group differences in quality of life (both tending to show within-group improvements). Interestingly, despite recent

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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 covers. It is possible that this difference in perception led to unblinding of individuals (i.e. believing that they must have the real covers 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 covers was not significantly different between the groups, and adherence (>70%) appeared to be at least as good, if not better than, with medications usually prescribed for asthma (e.g. inhaled corticosteroids ~50% (34)).

There are some other limitations to our study. All data on exacerbations and OCS use was reported by parents/carers and not confirmed by their primary care physician. However, we gathered information from parents on a 3 monthly basis and 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 from previous studies suggest that viruses and allergens in sensitised individuals act synergistically to increase the risk of asthma exacerbation and hospitalisation. As 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.

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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 have studied we estimate that approximately 8 children would need to be treated in order to prevent one child having any hospital attendances 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 might be younger, mono-sensitised children in non-smoking households, further research is required to clarify this.

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CONFLICTS OF INTEREST DISCLOSURES

Dr Murray has received grants from NIHR, JP Moulton Charitable Foundation and from North West Lung Research Centre Charity. She has received lecture fees from GSK and Novartis and travel grants from Novartis. Professor Custovic has received grants from Medical Research Council, JP Moulton Charitable Foundation and from North West Lung Research Centre Charity. He receives personal fees from AstraZeneca, Novartis, ThermoFisher and Regeneron / Sanofi. Professor Simpson has received grants from Medical Research Council, NIHR and EU FP7. She has received lecture fees from GSK, Chiesi and Thermofisher Scientific. Philip Foden, Helen Sumner and Elizabeth Shepley have no conflicts of interest.

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FIGURE LEGENDS

Figure 1. CONSORT (Consolidated Standards of Reporting Trials) flow diagram showing the participants' course during the study.

Figure 2. Proportion of children who suffered one or more severe exacerbation during the 12 month follow up period (for all children who completed 12 months Follow up, n=241). Results are shown for (A) one or more hospitalizations or ED visit 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).

Figure 3. Time to first hospitalizations or ED visit because of severe exacerbation of asthma. The model was adjusted for age, gender, ethnic group, maintenance asthma treatment, number of hospitalisations in the 12-month period prior to randomisation, index of multiple deprivation and tobacco smoke exposure. The risk was 45% lower in the Active compared with the placebo group (p=0.006).

Figure 4. Der p 1 levels in child's mattress (ng/m²) at recruitment and 12 months after intervention. Results are shown as geometric mean and 95% confidence interval for Active covers (mite-impermeable) (dashed line) and Placebo covers (solid line).

Preventing exacerbations by avoiding mite allergen

Figure 1.

Preventing exacerbations by avoiding mite allergen

Figure 2

A.

B.

Preventing exacerbations by avoiding mite allergen

Figure 3.

Number at risk

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

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Figure 4.

Preventing exacerbations by avoiding mite allergen

Table 1. Characteristics of study participants at randomisation.

*All children were skin test positive to house dust mite, but not all children completed skin test to other allergens. **Ascertained based on SPT or on symptom reports from parents and pet ownership/exposure.

	Placebo covers	Mite-impermeable Covers (Active)	P value
	N=138	N=146	
Age (mean; SD)	7.45 (3.55)	7.11 (3.49)	0.42
Age 3-10 yrs	106 (76.8%)	117 (80.1%)	0.50
Age 11-17 yrs	32 (23.2%)	29 (19.9%)	
Gender; male	94 (68.1%)	93 (63.7%)	0.43
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	41/134 (30.6%)	46/129 (35.7%)	0.38
Current eczema	71 (51.8%)	57/140 (40.7%)	0.07
Food allergy	26/130 (20.0%)	40/138 (29.0%)	0.09
Maternal asthma	43 (31.2%)	39/142 (27.5%)	0.50
Paternal asthma	30/134 (22.4%)	40/142 (28.2%)	0.27
Maternal smoking	35 (25.4%)	34/145 (23.4%)	0.71
Paternal smoking	31/133 (23.3%)	43/141 (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	138/138 (100%)	146/146 (100%)	

Preventing exacerbations by avoiding mite allergen

Table 1. Characteristics of study participants at randomisation (“Continued”)

Mite only	50/125 (40%)	60/130 (46.1%)	0.28
Cat	46/125 (36.8%)	46/130 (35.4%)	0.81
Dog	45/125 (36.0%)	44/130 (33.8%)	0.72
Grass	49/129 (38.0%)	46/136 (33.8%)	0.48
Aspergillus	8/126 (6.3%)	3/136 (2.2%)	0.09
Tree pollen	7/125 (5.6%)	4/135 (3.0%)	0.29
Number of allergens sensitised to excluding HDM (median; IQR)	N=131 1 (0-2)	N=135 1 (0-2)	0.55
Pet contact	58/137 (42.3%)	64/145 (44.1%)	0.76
Cat owner	22/137 (16.1%)	21/145 (14.5%)	0.71
Dog owner	31/137 (22.6%)	36/145 (24.8%)	0.66
Sensitised and exposed to pet**	29 (21.0%)	31 (21.2%)	0.96
GINA Step			0.98
GINA step 1-2	72 (52.2%)	76 (52.1%)	
GINA step ≥ 3	66 (47.8%)	70 (47.9%)	

Online data supplement for:

Preventing severe asthma exacerbations in children: A randomised trial of mite impermeable bedcovers

Clare S Murray, Phil Foden, Helen Sumner, Elizabeth Shepley, Adnan Custovic and Angela Simpson.

This supplement has been provided by the authors to give readers additional information about their work.

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Supplementary Methods

Dust sampling methodology.

1. Dust sample collection

Reservoir dust samples were collected from the living room floor and the child's mattress. Dust samples were collected by vacuuming a 1m² area using a Medivac dust sampler (airflow 45 l/s; Medivac Plc, Wilmslow, Cheshire, UK) for 2 minutes in a standardised fashion. The sampling head was loaded with a stainless steel mesh filter, to remove particles >300µm diameter, allowing a sample of fine dust to be collected onto a 5 µm pore size vinyl filter (Plastok Associates Ltd, Wirral, UK). Immediately after collection, the dust sample was transferred into a pre-weighed Petri dish and coded. The filled Petri dish was weighed to calculate the mass of fine dust collected and sample was stored at 4°C until extraction. After each sample collection the sampling head was cleaned using 70% isopropyl alcohol.

2. Extraction

A 100 mg aliquot of the dust was then extracted by rotation with 2 ml borate-buffered saline with 0.1% Tween₂₀ pH 8.0, at room temperature for 2 hours before being centrifuged for 20 minutes at 2500 rpm at 4°C. The supernatant was stored at -20°C until analysed for allergen content.

3. Measurement of house dust mite allergen

As the dominant mite species in the UK is *Dermatophagoides pteronyssinus*, we chose to measure the major allergen Der p 1 in the dust samples collected. In the UK, in previous studies *Dermatophagoides farina* accounts for ~ 0.5% of pyroglyphid mites collected and therefore Der f 1 was not measured ¹.

4. Der p 1 ELISA

All samples were assayed for content of major *Dermatophagoides pteronyssinus* allergen Der p 1 using monoclonal antibody (mAb) based ELISA (Indoor Biotechnologies, Cardiff, UK) using the technique described by Luczynska et al ²

Ninety-six well micro titre plates (Immulon II Dynatech) were coated with 100µl of mAb 5H8 (0.1ml of 1/1000 dilution 5H8 in 50 mM carbonate-bicarbonate buffer, pH 9.6), overnight at 4°C. The wells were then washed twice with phosphate buffered saline-0.05% Tween₂₀, pH 7.4 (PBS-T) and patted dry. The wells were then blocked by adding 100µl of 1% bovine serum albumin (BSA) PBS-T to each well and incubating for 30 minutes at room temperature. Each well was washed twice with PBS-T. 100µl of diluted dust samples (starting at 1 in 5) were added and the plates were incubated for 1 hour at room temperature. A control curve was

generated by adding doubling dilutions of the Universal Allergen Standard (containing 2500ng/ml Der p 1) ranging from 250 – 0.5ng/ml Der p 1 in 1% BSA, PBS-T. The wells were then washed 5 times with PBS-T, and then incubated with 100µl of diluted biotinylated anti-Der p 1 mAb 4C1(1/1000 dilution in 1% BSA, PBS-T) for 1 hour. The wells were washed 5 times with PBS-T and then incubated at room temperature for 30 minutes with 100µl Streptavidin Peroxidase (Sigma S5512, 0.25mg reconstituted in 1ml distilled water) diluted to 1/1000 with 1%BSA PBS-T. The wells were washed a further 5 times and the assays were developed by adding 100µl of 1mM azino-di(3 ethylbenzthiazoline sulfonic acid) (ABTS) in 70mM citrate phosphate buffer, pH 4.2 and 1/1000 dilution of H₂O₂. The plates were read using an Epoch™ Microplate Spectrophotometer (BioTek® Instruments, Inc., Vermont, USA) when the absorbance (405nm) reached 2.0-2.4.

Results were then calculated as µg Der p 1 per gram of fine dust collected (µg/g) or as total Der p 1 allergen collected (ng). The lower limit of detection for Der p 1 was 0.05µg/g.

Gina Steps

All guidelines can be downloaded at www.ginasthma.org

A summary of the GINA treatment steps are shown below for children/adolescents age 6+

	Preferred controller	Other controller options	Reliever
STEP 1	-	Consider low dose ICS	SABA as needed
STEP 2	Low dose ICS	LTRA	SABA as needed
STEP 3	low dose ICS/LABA	Med/high dose ICS; low Dose ICS +LTRA;	SABA as needed
STEP 4	Med/high dose ICS/LABA	+ LTRA; + theophylline	SABA as needed
STEP 5	Refer for add-on treatment	+ low dose OCS	SABA as needed

ICS: inhaled cortico-steroids; LABA: long acting beta agonist; med: medium dose; OCS oral corticosteroids; LTRA: leukotriene receptor antagonist; SABA: short acting beta agonist

ICS doses in Beclomethasone dipropionate or equivalent:

Low dose: < 5 years 200; 6-11 years 100-200mcg/day; 12+years 200-500/day

Medium dose: < 5 years 400; 6-11 years >200-400mcg/day; 12+years >500-1000/day

High does: 6-11 years >400mcg/day; 12+years >1000/day

Bedding Care instructions (given to all participants)

The bedding you have been provided with need not be washed. In the event of an accident or spillage on the bedding please wash at 40°C on a normal cycle. For assistance with any matter regarding the bedding please call the study team on 0161291xxxx

Index of multiple deprivation

Index of multiple deprivation (IMD) as a marker of socioeconomic status was calculated from the postcode (serves a similar function to US zip code; each postcode relates to on average 15 homes in a small geographic area) using <http://tools.npeu.ox.ac.uk/imd/>. Both the absolute value and the deprivation quintile group compared to national data for England were calculated.

Exploratory Subgroup Analyses

To identify characteristics of subjects most likely to respond to treatment we conducted subgroup analyses (not pre-specified) based on age, GINA step, sensitisation status, exposure to passive smoking and socioeconomic status.²² To assess whether any of the characteristics differed significantly between the randomisation groups in their effect on time to event, an interaction term was used. For each characteristic, the interaction term was added to the full multivariable Cox regression model and also to a model with just the characteristic and randomisation group.

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Figure E1 - Photographs of Encasings

Photographs of Active (Left) and Placebo (Right) encasings (a) normal view (b) 5-fold magnification and using Leica LMD 6000 Laser dissection microscope (c) 50 fold magnification, (d) 100 fold magnification

(a)

(b)

(c)

(d)

Supplementary Results

Table E1 - GINA classification of study participants at recruitment

GINA step	Placebo covers	Active covers (Mite-impermeable)
1	5 3.6%	10 6.8%
2	67 48.6%	66 45.2%
3	48 34.8%	49 33.6%
4	17 12.3%	21 14.4%
5	1 0.7%	0 0.0%

Table E2 - Der p 1 levels at recruitment in the Active and Placebo group.

Results are shown as concentration of allergen (µg/g) and total allergen recovered (ng/m²)

Dust reservoir	Placebo covers GM (95% CI)	Active covers (Mite-impermeable) GM (95% CI)	P-value
Der p 1 in living room floor (GM 95% CI, µg/g fine dust)	0.40 (0.29-0.56)	0.42 (0.31-0.58)	0.82
Der p 1 in living room floor (GM 95% CI ng/m ²)	51.66 (34.10-78.26)	53.77 (36.20-79.89)	0.89
Der p 1 in Child’s mattress (GM 95% CI µg/g fine dust)	1.06 (0.73-1.54)	1.62 (1.17-2.24)	0.09
Der p 1 in Child’s mattress (GM 95% CI ng/m ²)	167.57 (106.06-264.12)	298.03 (197.89-521.08)	0.06

Table E3 - Multivariable model of time to first emergency hospital attendance with a severe exacerbation of asthma.

Predictor	HR	95% CI	P value
Active covers (Mite impermeable) (compared to placebo)	0.55	0.36-0.85	0.006
Age (in years)	0.94	0.88-1.00	0.04
Female sex (compared to male)	0.98	0.63-1.54	0.94
GINA step (3 or above compared to below 3)	1.88	1.21-2.92	0.005
Ethnicity (non-white compared to white)	1.06	0.67-1.69	0.80
Number of asthma hospital admissions in previous 12 months	1.04	0.87-1.25	0.66
Index of multiple deprivation Rank (compared to Rank 1)			
Rank 2	0.39	0.12-1.31	0.03
Rank 3	0.42	0.14-1.29	
Rank 4	0.96	0.37-2.48	
Rank 5	1.20	0.47-3.02	
Tobacco smoke exposure	1.41	0.89–2.22	0.14

(If parents were unable to recall the exact date in the month when the event occurred, this was recorded as the 15th of that month. To ensure this did not result in bias, data was also analysed with the date set as 1st of the month and this did not alter the results.)

Figure E2 - Distribution of number of emergency hospital attendances in those who attended one or more times

Per Protocol Analysis

(Figures E3-E6), n=208

Figure E3 - Proportion of children who suffered one or more emergency hospital attendances for asthma.

Significantly fewer children in the Active covers (mite-impermeable) attended hospital with one or more severe asthma exacerbations compared to the Placebo covers (28/101 [27.7%] versus 44/107 [41.1%], $P=0.042$). There was no significant difference in the proportion of children in the Active and Placebo group who required one or more course of OCS for an asthma exacerbation (49/101 [48.5%] versus 54/107 [50.5%], $P=0.78$).

3A. Proportion of children who suffered one or more emergency hospital attendance with an asthma exacerbation

3B. Proportion of children who required one or more course of OCS for an asthma exacerbation.

Figure E4 - Time to first exacerbation requiring emergency hospital attendance

In the multivariable Cox regression analysis, this was significantly reduced in the Active covers (Mite-impermeable) compared with the Placebo covers (hazard ratio 0.46, 95% CI 0.28 to 0.76, P=0.002).

Number at risk								
Placebo	107	96	84	79	76	70	64	63
Active	99	96	89	85	79	76	74	74

Figure E5 - Time to first exacerbation requiring emergency hospital attendance in children aged 3-10 years

Following stratification by age, time to first exacerbation requiring emergency hospital attendance was longer in the active group in children aged 3-10 years (hazard ratio 0.42, 95% CI 0.23 to 0.75, $P=0.004$).

Number at risk

Placebo	80	71	61	56	55	52	47	46
Active	78	76	69	67	64	61	59	59

Figure E6- Time to first exacerbation requiring emergency hospital attendance in children aged 11-17 years

For children aged 11-17 years there was no difference in time to first exacerbation between groups (hazard ratio 0.57, 95% CI 0.16 to 2.06, P=0.39).

Number at risk								
Placebo	27	25	23	23	21	18	17	17
Active	21	20	20	18	15	15	15	15

Table E4 - Asthma control and quality of life questionnaire scores, compared between groups at each time point separately.

Measurements of asthma related quality of life and control were requested at 1 month, 4 month 8 months and 12 months by questionnaire, but completion rates were poor. For example for ACQ only 25 subjects in the Active group and 26 subjects in the placebo group completed the questionnaires at all time points. Furthermore, measurements could not be collected at baseline as all subjects had recently suffered an exacerbation as this was an inclusion criterion for the study; therefore it was not possible to adjust for baseline measures. PACQLQ and PAQLQ's high score indicates better quality of life (1-7). ACQ low score indicates better control (0-6).

Questionnaire	Time point	n	Placebo covers	n	Active covers (Mite-impermeable)	P value
PACQLQ	1 month	58	5.48(5.13-5.82)	62	5.44(5.09-5.79)	0.89
PACQLQ	4 month	56	5.77(5.43-6.11)	60	5.84(5.47-6.21)	0.79
PACQLQ	8 month	47	5.89(5.51-6.27)	54	5.79(5.41-6.18)	0.72
PACQLQ	12 month	112	6.15(5.93- 6.36)	113	6.15(5.93-6.37)	0.99
mini PAQLQ	1 month	24	5.62(5.01-6.23)	26	5.31(4.78-5.83)	0.43
mini PAQLQ	4 month	21	5.92(5.40-6.44)	19	5.56(4.98-6.13)	0.33
mini PAQLQ	8 month	19	5.81(5.15-6.47)	16	5.69(5.03-6.36)	0.80
mini PAQLQ	12 month	25	6.03(5.57-6.50)	17	6.20(5.84-6.57)	0.57
ACQ	1 month	59	1.15(0.90-1.41)	62	1.20(0.86-1.54)	0.83
ACQ	4 month	56	0.88(0.60-1.17)	59	0.88(0.57-1.18)	0.97
ACQ	8 month	39	0.79(0.48-1.11)	49	1.0(0.65-1.33)	0.40
ACQ	12 month	108	0.83(0.60-1.06)	112	0.67(0.50-0.85)	0.29

Table E5 - Acceptability of encasings

(n=232, collected between 8 and 12 months into the intervention, by a researcher blind to group allocation)

	Placebo covers	Active covers (Mite-impermeable)	P value
Duvet slipped within encasing	5.3%	32.2%	<0.001
Encasing was noisy	0.9%	14.4%	<0.001
Encasing made them too warm	1.8%	3.4%	0.64
Encasing uncomfortable	1.8%	26.3%	<0.001
Considered removing the bedding	2.6%	25.4%	<0.001
Of those using the bedding at the end of the study - stated they would continue to use after the study had finished	89.4%	87.3%	0.68

Figure E7 - Der p 1 levels in lounge floor (ng/m2) at recruitment and 12 months after intervention.

Results are shown as geometric mean and 95% confidence interval for Active covers (mite-impermeable) (green dashed line) and Placebo covers (blue solid line)

ITT Subgroup Analysis

Table E6 -Time to first emergency hospital attendance with a severe exacerbation of asthma - Subgroup analysis.

Hazard ratios are for Active group compared with the placebo group (Multivariable models, with HR for other variables not shown)

Characteristic on which groups were stratified	n	HR	95% CI	P value
children aged 3-10 years	212	0.54	(0.33-0.87)	0.006
children aged 11-17 years	60	0.96	(0.33-2.80)	0.94
children aged 3-5 years	114	0.58	(0.31-1.09)	0.09
children aged 6-11 years	118	0.47	(0.22-1.00)	0.05
children aged 12-17 years	40	0.50	(0.13-1.98)	0.32
Sensitised only to mite *	102	0.48	(0.23-0.98)	0.04
Sensitised to mite and other allergens	157	0.64	(0.35-1.17)	0.14
Non- Smoking home	153	0.49	(0.26-0.90)	0.02
Any smoker in the home	119	0.75	(0.40-1.43)	0.39
GINA Step 1-2	139	0.61	(0.31-1.21)	0.16
GINA Step 3-5	133	0.52	(0.30-0.94)	0.03
Deprivation score in lowest Quintile of national reference data	130	0.48	(0.27-0.85)	0.01
Deprivation score in Quintiles 1-4 of national reference data	142	0.83	(0.43-1.59)	0.57

* Children who were not skin tested to the whole panel of allergens were excluded from this analysis (n=15)

Figure E8 - Time to first exacerbation requiring emergency hospital attendance in children age 3 to 10 years

The risk of hospital presentation was significantly lower in the active group than the placebo group (HR 0.54 [0.33-0.87], p=0.012).

Number at risk								
Placebo	104	90	78	68	65	58	53	52
Active	108	103	95	88	82	73	70	70

Figure E9 - Time to first prednisolone use in children aged 3-10 years

In the age-stratified analysis, the risk of prednisolone use was lower in the Active group amongst children aged 3-10 years (hazard ratio 0.69, 95% CI 0.46 to 1.04, $P=0.077$), but failed to reach significance.

Number at risk

Placebo	104	87	72	63	59	52	48	45
Active	108	99	89	79	70	56	55	54