

Comparative Effectiveness Review Disposition of Comments Report

Research Review Title: Effectiveness of Indoor Allergen Reduction in Management of Asthma

Draft review available for public comment from April 26, 2017 to May 25, 2017.

Research Review Citation: Leas BF, D'Anci KE, Apter AJ, Bryant-Stephens T, Schoelles K, Umscheid CA. Effectiveness of Indoor Allergen Reduction in Management of Asthma. Comparative Effectiveness Review No. 201. (Prepared by the ECRI Institute–Penn Medicine Evidence-based Practice Center under Contract No. 290-2015-0005-I.) AHRQ Publication No. 18-EHC002-EF. Rockville, MD: Agency for Healthcare Research and Quality; February 2018. Posted final reports are located on the [Effective Health Care Program search page](http://effectivehealthcare.ahrq.gov/topics/asthma-nonpharmacologic-treatment/final-report-indoor-allergen-reduction). DOI: <http://doi.org/10.23970/AHRQEPCCER201>.

Comments to Research Review

The Effective Health Care (EHC) Program encourages the public to participate in the development of its research projects. Each research review is posted to the EHC Program Web site or AHRQ Web site in draft form for public comment for a 3-4-week period. Comments can be submitted via the Web site, mail or E-mail. At the conclusion of the public comment period, authors use the commentators' submissions and comments to revise the draft research review.

Comments on draft reviews and the authors' responses to the comments are posted for public viewing on the Web site approximately 3 months after the final research review is published. Comments are not edited for spelling, grammar, or other content errors. Each comment is listed with the name and affiliation of the commentator, if this information is provided. Commentators are not required to provide their names or affiliations in order to submit suggestions or comments.

The tables below include the responses by the authors of the review to each comment that was submitted for this draft review. The responses to comments in this disposition report are those of the authors, who are responsible for its contents, and do not necessarily represent the views of the Agency for Healthcare Research and Quality.

Archived: This report is greater than 3 years old. Findings may be used for research purposes, but should not be considered current.



Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 1	General Comments	This manuscript details two separate and unrelated evaluations of effectiveness of asthma interventions. The first section is focused on the role of allergen reduction and the second on bronchial thermoplasty. The article is generally well written and goes through the pertinent data appropriately; however, there are major concerns about the findings—especially in regard to the allergen reduction section. The authors conclude (in their key messages) that “single interventions designed to reduce indoor allergen exposure may have little effect on asthma outcomes.” This is an unfortunately biased representation of their findings. In fact, the overall outcome is that there are not enough good studies to provide any really appropriate recommendations for or against single (or even multiple) interventions. This should permeate throughout the document with regard to allergen reduction.	Thank you for your comments. We have revised the text in the Key Points, Results, and Discussion to clarify the distinction between a lack of evidence, and evidence for no effect.
Peer Reviewer 1	General Comments	To my read, the major take home message is that the studies in these areas are in desperate need of new research studies that are appropriate designed and implemented (allergen reduction being the worst of the two). This seems to be the important take home message for NHLBI, but it is garbled and lost throughout the text, and appears to just suggest that individuals with asthma should undergo bronchial thermoplasty before considering allergen reduction. This is an unfortunate outcome of the writing bias (as mentioned above) and the juxtaposition of the two disparate issues together in the same report.	Thank you for your review and feedback. We have separated the document into two distinct reports for clarity and ease of use. We agree that new studies are needed that address these interventions, and we emphasize that need in the future research needs sections of both reports.
Peer Reviewer 2	General Comments	This is a very well-written report that contains a thorough analysis of non-pharmacologic interventions for asthma. The target populations and audience are clearly defined, and key questions clearly articulated.	Thank you for your review and feedback.

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Peer Reviewer 4	General Comments	Thank you for the opportunity to review the draft of “The Effectiveness of Indoor Allergen Reduction and the Role of Bronchial Thermoplasty in the Management of Asthma.” The manuscript is very well written and the methods used including the study inclusion and exclusion criteria and the judgment of the significance of evidence were very rigorous. The goals of the review are well stated. However, the form is very dry and quite difficult to follow. The frequent use of acronyms requires constant referral to the glossary.	Thank you for your review and feedback. We have separated the document into two distinct reports, and reduced the use of acronyms, for clarity and ease of use.
Peer Reviewer 4	General Comments	Generally, the conclusions for the home intervention studies align with the thoughts of many individuals in the field. Namely, that single intervention studies have little likelihood of demonstrating clinical improvement. However, targeted multi component interventions when performed properly and coupled with education can reduce symptoms and provide improved clinical outcomes.	Thank you.
TEP Reviewer 1	General Comments	This is a well-written systematic review of two key question areas, the effects of allergen remediation in the home to improve asthma and the effects of bronchial Thermoplasty, BT, to improve asthma. There are a few points and clarifications that would be useful for the clinician in understanding the results of these analyses. Those are listed below.	Thank you for your review and feedback.
TEP Reviewer 2	General Comments	Overall, the manuscript is written well and is the product of a substantial amount of work and is timely.	Thank you for your review and feedback.
TEP Reviewer 3	General Comments	Combining allergen reduction and BT in a single report is not intuitive. Would suggest a statement in the report (likely in Intro) as to why these 2 unrelated therapies are being presented together.	Thank you for your review and feedback. We have separated the document into two distinct reports for clarity and ease of use.

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TEP Reviewer 4	General Comments	I have one major comment In the discussion, I think it is critical to discuss that the home environment is not the only place that adults and children are exposed to environmental inhalant allergens. Children and adults spend significant amounts of time in school and at work and information about exposures at these locations is not known. This could create so much noise that the effectiveness of home environmental control measures could be washed out and it could account for some of the variability and inconsistency in the results of interventions.	Thank you for your review and feedback. We agree that school and work environments play an important role in asthma morbidity, and studies conducted in those settings were eligible for our review. However, we did not identify any school or work-based studies that met our complete inclusion criteria. We have added the following text to the Discussion emphasizing this important limitation of the “Another important factor is the potential exposure to indoor allergens outside the home. Patients with asthma may be exposed to allergens at work or school or while engaged in other activities. Such exposure may limit the effectiveness of interventions that are implemented only at home. This review was designed to include studies that evaluated interventions in work or school environments, but we did not identify any studies that fit those criteria.”
TEP Reviewer 5	General Comments	It was unclear to me why these 2 very different questions were lumped together.	Thank you for your review and feedback. We have separated the document into two distinct reports for clarity and ease of use.
TEP Reviewer 5 Michael Wechsler	General Comments	Report is clinically meaningful with regard to key question 1 and accurate.	Thank you.
TEP Reviewer 6	General Comments	The report is highly meaningful to a clinical audience. The interventions studied are commonly recommended in clinical practice yet the evidence base is limited. Synthesis of the literature is quite valuable and sheds light on opportunities for further studies. The findings also support a multi-interventional approach.	Thank you for your review and feedback.

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Public Reviewer 1 Rhonda Vosmus	General Comments	After review of the single removal of allergens and single refining/mitigating sources, I remain with my original messages to patients and families, "it is the multipronged approach to reducing known allergens that is most effective in improving quality of life, least amount of medications and reduced need for medications."	Thank you for your comments.
Public Reviewer 3 Rubin Cohen on behalf of AACP-CHEST	General Comments	The report is well done. I would suggest separating the 2 topics under 2 subheadings in the abstract and in conclusions	Thank you for your comments. We have separated the document into two distinct reports for clarity and ease of use.
Public Reviewer 6 Tonya Winders on behalf of the Allergy and Asthma Network	General Comments	We applaud the AHRQ on this systematic review and believe both of these issues are important updates advance asthma care.	Thank you for your comments.
Public Reviewer 7 Susan Rappaport on behalf of the American Lung Association	General Comments	The American Lung Association appreciates the opportunity to submit comments with regard to the Agency for Healthcare Research and Quality (AHRQ) draft report for Effectiveness of Indoor Allergen Reduction and the Role of Bronchial Thermoplasty in the Management of Asthma, conducted by AHRQ's Evidence-Based Practice Center Program. The American Lung Association is the leading organization working to save lives by improving lung health and preventing lung disease through education, advocacy and research. The organization represents lung disease patients, their families, loved ones and caregivers. The Lung Association appreciates the analysis conducted with this report and provides the following comments.	Thank you for your comments.
Public Reviewer 7 Susan Rappaport on behalf of the American Lung Association	General Comments	It might be more effective to separate these two analyses on allergens and BT within the document itself, or consider making two separate documents.	We have separated the document into two distinct reports for clarity and ease of use.
Public Reviewer 7 Susan Rappaport on behalf of the American Lung Association	General Comments	The Lung Association respectfully thanks the AHRQ for conducting this report. We thank you for the opportunity to submit our comments and for your consideration.	Thank you.

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Public Reviewer 8 Robert Barker on behalf of the American Fiber Manufacturers Association (AFMA)	General Comments	The American Fiber Manufacturers Association (AFMA) supports and endorses the evidence provided and views expressed in the Scientific Information Package (SIP) being submitted by the Carpet and Rug Institute (CRI) regarding the review report “Effectiveness of Indoor Allergen Reduction and the Role of Bronchial Thermoplasty in the Management of Asthma” and, in particular, Key Question #1. AFMA is the U.S. national trade association for producers of manufactured fiber. The sector has an estimated annual output of over \$20 billion, serving markets across the American economy’s manufacturing and consumer platforms. Within this array, fiber-based floor coverings, upholstery, and other products used in residences, offices, and public spaces comprise the largest sector.	Thank you for your comments. We carefully reviewed the information contained in the Scientific Information Package while conducting our research.

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Public Reviewer 9 Joe Yarbrough on behalf of the Carpet and Rug Institute (CRI)	General Comments	<p>The following comments are submitted on behalf of the members of the Carpet & Rug Institute (CRI). By way of background, CRI is a nonprofit trade association representing the manufacturers of more than 95 percent of all carpet made in the United States, as well as their suppliers and service providers. Based in Dalton, Georgia, CRI is an evidence-based source for data and research regarding carpet and rugs. CRI coordinates with other stakeholders to help meet the needs of consumers and to promote an understanding of the scientific and environmental data on carpet and soft floor coverings.</p> <p>The following comments are in response to the Agency for Healthcare Research and Quality's (AHRQ) Draft Report titled "The Effectiveness of Indoor Allergen Reduction and the Role of Bronchial Thermoplasty in the Management of Asthma." CRI will restrict these comments to the issue of the effectiveness of indoor allergen reductions addressed by Key Question 1 (KQ1) in the Draft Report.</p> <p>Current federal guidelines "recommend" the removal of carpet to reduce animal allergens within the home, and present the removal of carpet as an "action to consider" to control dust mites in the home setting. CRI has strongly urged the removal of these outdated recommendations as soon as possible, based on the most current scientific evidence. The statements and recommendations concerning carpeting within the 2007 guidelines developed by the National Heart, Lung and Blood Institute (NHLBI) may also inadvertently cause more harm than good for children and other individuals suffering from asthma.</p> <p>It is particularly important to ensure that the information in federal guidelines is accurate, evidence-based, and up-to-date. As noted by NHLBI, federal guidelines are used by a large number of public and private stakeholders, including other federal and state agencies. Health professionals rely on federal materials as a trusted source of information when communicating information to their patients. Families and school districts follow recommendations in the guidelines when</p>	Thank you for your comments.
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		making purchasing and building decisions. State and local governments mimic federal guidance in their own materials and public documents. Therefore, it is vitally important to the public health that the guidelines be based on the most current and strongest scientific evidence. This evidence must be accurately interpreted to guide health professionals to help reduce the burden of asthma attacks on affected individuals and the health care system.	
Public Reviewer 9 Joe Yarbrough on behalf of CRI	General Comments	CRI commends AHRQ for developing this Draft Report in order to evaluate the effectiveness of indoor allergen reduction interventions on asthma outcomes—particularly the effectiveness of carpet removal as an intervention to reduce or remove exposure to indoor inhalant allergens on asthma control, exacerbations, and quality of life. CRI notes that many of the Draft Report's findings concerning carpet removal are in line with the most current scientific data. The data considered in the Draft Report no longer supports the recommendations found in the 2007 guidelines. Thus, we encourage the Agency to finalize this Draft Report with the suggested modifications described above so that much-needed updates to current asthma guidelines can be made without delay.	Thank you for your comments.

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Public Reviewer 11 David Peden on behalf of the American Academy of Allergy, Asthma and Immunology (AAAAI)	General Comments	<p>Established in 1943, the American Academy of Allergy, Asthma & Immunology (AAAAI) is a professional organization with more than 7,000 members in the United States, Canada and 72 other countries. This membership includes allergist/immunologists (A/I), other medical specialists, allied health and related healthcare professionals—all with a special interest in the research and treatment of patients with allergic and immunologic diseases. On behalf of this membership, please accept the following comments regarding the Draft Report, <i>“The Effectiveness of Indoor Air Allergen Reduction and the Role of Bronchial Thermoplasty in the Management of Asthma”</i>.</p> <p>Academy leadership notes that the manuscript is well written, the product of a substantial amount of work and time. Academy leadership further notes that the group explained the various choices made by analysis very effectively. Academy leadership commends the research group for a careful and organized approach in addressing these two questions, and offers these further comments for their consideration.</p>	Thank you for your comments.



Public Reviewer 12 Melanie Carver on behalf of the Allergy and Asthma Foundation of America (AAFA)	General Comments	<p>The Asthma and Allergy Foundation of America (AAFA), a not-for-profit organization founded in 1953, is the leading patient organization for people with asthma and allergies, and the oldest asthma and allergy patient group in the world. As the premier patient organization, AAFA offers education, advocacy and research services to help people live a life without limits.</p> <p>We appreciate the opportunity to address AHRQ's Draft Comparative Effectiveness Review of Indoor Allergen Reduction.</p> <p>There are currently 24 million people in the US living with asthma and over 50 million people living with allergies. Around 2/3 of people with asthma have allergic triggers. Allergen reduction is a recommended asthma management strategy by many leading experts and organizations, including AAFA.</p> <p>AAFA's Wee Wheezers at Home program was selected by the Centers for Disease Control and Prevention's National Center for Environmental Health (CDC-NCEH) for inclusion in its list of "Effective Interventions for Asthma Control," which is available on the CDC-NCEH website: www.cdc.gov/asthma/interventions/children_medicalclinics.htm.</p> <p>Wee Wheezers at Home and its derivative products (Wee Breathers) are home-based asthma education programs for parents of children with asthma. Wee Wheezers at Home emphasizes specific content areas, including trigger avoidance (allergen avoidance). It was evaluated in a controlled trial of 95 families (Brown, Bakeman, Celano, Demi, Kobrynski and Wilson, 2002). Outcome measures included symptom-free asthma days as reported by parents, parental sleep interruption, degree to which child was bothered by asthma symptoms, and the number of days child was</p>	<p>Thank you for your comments. Although we did not assess the Wee Wheezers at Home program because interventions that are focused on patient education are outside the scope of this review, we agree that educational efforts are a critical component of asthma management.</p>
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	<p>sick due to asthma. Children in the treatment group experienced improvement on all five outcomes.</p> <p>Low-income and minority children bear the heaviest burden of asthma. In order to address the needs of these children and their families, AAFA conducted a needs assessment within asthma education programs and home visitor and child care services. The asthma education program review identified 118 relevant home visitor programs across the US. The home visitors always conducted a visual environment assessment for asthma triggers, but far fewer conducted any remediation or testing for asthma triggers. After careful review and analysis of all the data collected during the needs assessment, AAFA created Wee Wheezers at Home and Wee Breathers to meet the needs identified by home visitors and child care providers. The result is an asthma-education program with multiple components, including an environmental checklist for homes and child care centers. Multi-factorial allergen avoidance is a key message in these programs.</p> <p>Americans spend an estimated \$10 billion a year on non-medicinal, consumer products marketed for people with asthma and allergies such as vacuum cleaners, air cleaners, bedding, toys, flooring, and more. Often these products advertise a wide variety of features and benefits including suitability for those with asthma and allergies, the ability to prevent allergen accumulation, and in some extreme cases, promising improved health for consumers without providing scientific proof or validation for such claims. The allergen-avoidance market continues to grow as a result of increased consumer demand, but "currently there is little or no regulation governing claims".</p> <p>In 2006, the asthma & allergy friendly® Certification Program was created by AAFA in partnership with Allergy Standards Limited (ASL, with the mission to empower consumers to make an informed purchase</p>	
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		<p>decision when choosing allergen-avoidance products. The Certification Program independently tests and identifies consumer products that are more suitable for the 60+ million people in the United States living with asthma and allergies.</p> <p>The asthma & allergy friendly™ Certification Standards support the overall concept of an allergen avoidance plan for people with asthma and allergies.</p> <p>AAFA and ASL develop certification standards for each product type after a review and agreement by an independent Medical Review Panel. Only products that meet these strict requirements receive asthma & allergy friendly certification.</p>	
Public Reviewer 12 Melanie Carver on behalf of AAFA	General Comments	AAFA has concerns that the Draft Comparative Effectiveness Review of Indoor Allergen Reduction seems to equate the lack of appropriate studies on single interventions with a lack of efficacy. AAFA respectfully supports and encourages additional research on the effectiveness of single and multicomponent allergen reduction methods.	We have revised the text in the Key Points, Results, and Discussion to clarify the distinction between a lack of evidence, and evidence for no effect. We agree that more research is necessary to address many of these areas.
Peer Reviewer 2	Introduction	No concerns.	Thank you.
Peer Reviewer 3	Introduction	The material as it stands is appropriately introduced.	Thank you for your review and feedback.
Peer Reviewer 4	Introduction	This is very short. A little history and creative writing here would reimburse the reader to a small extent for the dry, grinding work to come.	We hope that dividing the review into two separate reports improves its readability and usefulness. We attempted to write succinct, focused introductory sections that are consistent with other evidence reviews conducted to support updated NHLBI guidelines.
TEP Reviewer 1	Introduction	On page 1 of the report, pollen is listed as an indoor allergen.	We have removed the reference to pollen.

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TEP Reviewer 1	Introduction	It might be useful in the introduction to delineate the differences between allergen sensitization and true allergy. There was a lack of discussion regarding whether individuals had allergic asthma or asthma with allergic sensitization based on a skin test which may or may not be accurate.	We agree that this is an important point, and we have addressed this in more depth in the revised Results and Discussion sections.
TEP Reviewer 3	Introduction	Succinct. As noted in General Comments: Combining allergen reduction and BT in a single report is not intuitive. Would suggest a statement in the report as to why these 2 unrelated therapies are being presented together.	We have separated the document into two distinct reports for clarity and ease of use.
TEP Reviewer 5	Introduction	Appropriate	Thank you.
TEP Reviewer 6	Introduction	Very well written and clear. The report clearly states the two key questions and the analytical framework applied. Figure 1 is quite helpful	Thank you.
Public Reviewer 2 William Busse	Introduction	Both reviews were extensive and conclusions supported by available evidence. Data indicate little benefit from allergic avoidance. No studies on carpet removal.	Thank you for your comments.

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Peer Reviewer 1	Methods	1. For allergen reduction interventions (KQ1) there is a major problem with the studies chosen and the subjects involved. In particular, any allergen reduction strategy would be expected to only work on those individuals who are sensitized AND allergic to the allergen. Unfortunately, the studies chosen for KQ1 fail in this regard. Approximately 40% of the studies did not demonstrate any sensitivity to the allergens being reduced — these studies really should not be considered at all. The other studies demonstrated at least some evidence of sensitization to at least one allergen being reduced. However, this is really insufficient, as well. Ideally a study would show that the subject is symptomatic when exposed to the allergen, and then examine the effect of allergen reduction on asthma, etc. None of the studies included (and in fact, no study that has been done that I'm aware of) actually uses this methodology. However, it is important to clearly and distinctly state this in the report. The failure of allergen reduction strategies to work may simply be due to a failure to be using them on the appropriate population (and/or inappropriate randomization of subjects within these studies due to this issue — and raises questions about the studies where “the majority” of subjects were sensitized to the allergen; were the subjects properly randomized then?)	We agree that sensitization and allergic reaction are of great importance in evaluating the effectiveness of interventions. We have added text to the Results and Discussion sections to emphasize these issues. Our analysis also found that 40 out of 60 RCTs reported that all enrolled patients were sensitized to an allergen targeted by their respective interventions, and ninety percent of the RCTs (54 of 60) reported that at least a majority of patients had positive tests confirming sensitization. Moreover, 43 studies confirmed sensitization using skin prick tests, while 13 used blood tests. However, studies uniformly did not report whether patients had demonstrated allergic reaction beyond skin prick tests or serum IgE measurements. We now acknowledge in the Discussion that inclusion of non-sensitized patients, as well as lack of data regarding actual allergic reaction to indoor allergens, are important limitations of the evidence base.
Peer Reviewer 1	Methods	2. The authors should be aware that blood tests are less reliable than skin tests (epicutaneous testing, not intradermal) at indicating if a subject is likely to be allergic (i.e., symptomatic upon exposure). I would recommend they look at the recent NIAID Food Allergy guidelines in this regard. Again, relying just on sensitization is insufficient to properly identify those subjects who would be expected to improve with the treatment.	.We have added text to the Results and Discussion describing how many studies used skin tests versus blood tests. We also added a discussion of the limitations of the evidence base that result from the use of sensitization rather than allergic reaction to enroll patients, including the use of less precise tests to identify patient sensitization.

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Peer Reviewer 1	Methods	3. The general recommendation for dust mite avoidance is the use of dust mite proof encasings and washing bedding in at least 130F water weekly (it has been demonstrated that below 130F the dust mites are not killed). It may be beneficial to note that most of the studies reported did not adhere to this clinical practice.	Some of the studies advised patients on how to launder bedding. However, as you note, adherence to this or any other allergen avoidance practice is rarely measured. We have added text to the Discussion addressing this limitation.
Peer Reviewer 1	Methods	4. The complications chosen as “asthma-related” are somewhat unusual — especially a myocardial infarction and steroid-induced hypoglycemia (are you sure this wasn’t supposed to be hyperglycemia?) More details as to why these were chosen, etc., would be beneficial.	Thank you for noticing the error with hyperglycemia; we have corrected that. The complications were selected with input from the Technical Expert Panel and the asthma clinicians on our study team, and were intended to include common complications of asthma or asthma management as well as rare but serious events that may occur in patients with asthma.
Peer Reviewer 1	Methods	5. It is important to acknowledge the impossibility of performing a blinded pet removal study. It is understandable that there are specific requirements for studies to be included in this analysis; however, by nature, this report would be unable to demonstrate a clear effect of allergen control with pets because the study would require removing the pets from the home — something that just could not be done in a blinded fashion. As a result, there are no good studies/data to support (or refute) pet removal. This is a problem with study choice and not due to an apparent lack of effect of the intervention.	We acknowledge the difficulty in performing blinded studies, and we did not restrict our analysis to studies that were blinded or randomized. We have added to the report one study of pet removal that was not randomized but did have a control group. We did not identify any other studies that evaluated pet removal and included a control group.
Peer Reviewer 2	Methods	Study selection and inclusion/ exclusion criteria seemed appropriate.	Thank you
Peer Reviewer 2	Methods	This is a fast-moving field, and ongoing studies on both allergen reduction and BT are underway and should be published in next few years. At this point I could not find applicable studies that were missed.	Thank you.

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Peer Reviewer 2	Methods	Please explicitly define the GRADE criteria approach.	We have expanded our discussion of how individual studies and the overall evidence base were assessed, based on the AHRQ EPC methods, in the Methods section.
Peer Reviewer 3	Methods	Somehow the approach missed some I think important material	Thank you for your comments.
Peer Reviewer 4	Methods	For the multi component studies, your stated approach of organizing your strength of evidence analysis by grouping according to the primary active component used in the study I see as a problem. This approach tends to weaken the impact of the studies that used multiple interventions tailored to the needs of the family.	We undertook four different approaches to attempt to analyze the multicomponent studies. First, we attempted to group the studies into “bundles” based on shared components, but this was not feasible because the specific combinations of interventions were too diverse. Then we compared studies that had positive findings with studies that had no effect, and attempted to identify differences between the interventions used, but this analysis did not detect any patterns associated with positive results. Since these approaches did not enable further analysis, we evaluated the studies by active component, which provided a more useful framework. We agree that this strategy limits the robustness of our evaluation, and we note this limitation in the report. During peer review we also conducted a Qualitative Comparative Analysis to augment the analysis. All of these approaches are now described more fully in the Results, and the limitations of our analysis is addressed in the Discussion.

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TEP Reviewer 1	Methods	In the methods section for the allergen reduction part of the paper, I agree that there is difficulty in combining studies due to different outcomes. However, perhaps just as important is the differences in inclusion and exclusion criteria used for the patient populations. In addition to different age ranges, severity and control of asthma at randomization would be critical.	These are important factors to consider, and we documented those aspects of the included studies in the evidence tables in the Appendix. We also added text to the Discussion noting the importance of asthma control and disease severity in detecting the effect of allergen reduction interventions. We also emphasized that a major limitation of the evidence base is the heterogeneity of patient populations across studies, as well as a lack of detailed information about asthma control and severity in many studies.
TEP Reviewer 2	Methods	In studies that enroll low-income urban populations, the most commonly used primary outcome is days of symptoms, which is ascertained by questionnaire and not a daily symptom diary. This type of outcome has been used for decades in studies enrolling this population and although not on the list of formally validated outcomes, has face validity given its performance in this population over many many years. In fact, the "validated" measures of symptoms and quality of life have not been validated in this population and there are reasons to be concerned that they perform differently in low income minority populations that the populations for which they were validated. It seems that the studies that used these type of outcomes were downgraded in importance because of the definition of acceptable outcomes that was developed. This definition should be reconsidered.	The outcomes were selected to focus on validated and relevant asthma measures that are consistent with existing frameworks for assessing asthma outcomes, as proposed in Busse et al. (Journal of Allergy and Clinical Immunology, 2012, 129:S1-8). Although symptom days are often used as a primary outcome in published studies, they do not represent a validated or standardized metric. We did, however, grade the evidence for symptoms for each intervention, using the same methods that were applied to the other outcomes, and found almost no high or moderate strength evidence demonstrating improvement in symptom days.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer 3	Methods	Pg 6 - line 32 - stating all patients had diagnosis of "allergic asthma" does not appear correct. Certainly not for the BT studies which did not require allergy. This is an example of problems combining allergen reduction and BT in a single report.	We have removed "allergic" from that sentence, and have created two separate reports.
TEP Reviewer 3	Methods	I/E criteria are appropriate and justifiable. Methodologies explained well.	Thank you.
TEP Reviewer 4	Methods	In the search strategy (Methods Search Strategy, Page 14 of 173), I would include that studies that did not include the allergic status of participants were included in the analysis. Perhaps this should also be included in Table 1.	We have added text in the Methods clarifying that the allergic status of patients was not a requirement for study inclusion, and address this as a limitation in the Discussion.
TEP Reviewer 4	Methods	In Table 1 under comparators (16 of 173), it is not clear to me how reduction or elimination of exposure to multiple indoor inhalant allergens could serve as a comparator group. Isn't that an intervention group?	Those comparators refer to the possibility of head-to-head comparisons between interventions, as opposed to studies controlled by no intervention or by a placebo. An active comparator is often the most appropriate comparator.
TEP Reviewer 4	Methods	Table 1. under outcomes (17 of 173): what about non RSV bronchiolitis, acute/chronic bronchitis (non-CF), flu as asthma-related complications for hospitalization?	The complications were selected with input from the Technical Expert Panel and the asthma clinicians on our study team, and were intended to include common complications of asthma or asthma management as well as rare but serious events that may occur in patients with asthma.
TEP Reviewer 4	Methods	Table 1 under setting (17 of 173): Does this include home child care as well?	Home care settings were eligible for inclusion, although we did not find any studies that fit our other inclusion criteria.



Commentator & Affiliation	Section	Comment	Response
TEP Reviewer 4	Methods	Under data synthesis (18 of 173): How was an absolute 10% difference (between groups etc) chosen for the SOE tables?	We used established thresholds identified in published literature for assessing clinically important differences for several important outcome measures. These thresholds are documented in a new Appendix E. However, for most of the asthma outcomes for which improvement was reported, thresholds are not established. The 10% “rule of thumb” was selected by the study team methodologists as a basic, standardized criterion for identifying clinical differences in measures for which we did not identify existing thresholds.
TEP Reviewer 4	Methods	In the Strength of the Body of Evidence (18 of 173). I had to keep reminding myself what high strength of a negative result meant. It would have been helpful to me in this section to explain the two most common SOE assessments (high SOE, neg result, low SOE positive result).	We have attempted to clarify the practical meaning of the strength of evidence assessments throughout the report.
TEP Reviewer 5	Methods	More recent literature is not included. This is a weakness. Guidelines are so out of date, the most recent literature should be considered in this guideline update. Literature covered is almost 1 year old for this dynamic field.	During peer review, we updated our searches and identified four additional studies that fit our inclusion criteria.



Commentator & Affiliation	Section	Comment	Response
TEP Reviewer 5	Methods	For outcomes, the order seems inappropriate. Most generally consider exacerbations as a key outcome. It is reported second to asthma control and there should not be prioritization based on alphabet.	The selection of outcomes was designed to focus on validated and relevant asthma measures that are consistent with existing frameworks for assessing asthma outcomes, as proposed in Busse et al. (Journal of Allergy and Clinical Immunology, 2012, 129:S1-8). We chose five primary outcomes for assessment: asthma control, exacerbations, healthcare utilization, quality of life, and pulmonary physiology. Our analysis did not weight any of these primary outcomes above another, although we did prioritize these ahead of the secondary outcomes of asthma symptoms and allergen reduction...
TEP Reviewer 5	Methods	Also, the assessment of evidence when there are few studies, even if well done, reflexes to LOW. This should not be the case.	As described in the Methods, we used AHRQ EPC methods to guide our assessment of the body of evidence. When the body of evidence is small, such as a single trial with an inadequate sample size, or a few trials with small patient populations, we may downgrade the evidence based on imprecision. Additionally, even when studies are well-designed and exhibit low risk of bias, we may also reduce the strength of evidence based on concerns about consistency, directness, or publication bias.
TEP Reviewer 6	Methods	Clear and well written. Attempts were made to include gray literature. Studies were selected according to a pre-specified framework, and this is a major strength.	Thank you.
Public Reviewer 3 Rubin Cohen on behalf of AACP- CHEST	Methods	No issues	Thank you.

Source: <https://effectivehealthcare.ahrq.gov/topics/asthma-nonpharmacologic-treatment/final-report-indoor-allergen-reduction>

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Commentator & Affiliation	Section	Comment	Response
Public Reviewer 9 Joe Yarbrough on behalf of CRI	Methods	We commend AHRQ for conducting this systematic review of the current and best available scientific information to better address the effectiveness of indoor allergen reductions, including carpet removal, raised by Key Question 1 (KQ 1). The Draft Report acknowledged the challenges associated with undertaking research in this area. Often, single interventions do not result in any measurable changes in asthma outcomes. Multicomponent interventions create challenges because one cannot identify the most effective intervention in this type of study. Given the challenges associated with this body of research, we strongly support the methodology used in the Draft Report to only include high quality interventional studies. The use of high quality studies minimizes the risk of bias and misinformation.	Thank you.

Source: <https://effectivehealthcare.ahrq.gov/topics/asthma-nonpharmacologic-treatment/final-report-indoor-allergen-reduction>

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Commentator & Affiliation	Section	Comment	Response
Public Reviewer 11 David Peden on behalf of AAAAI	Methods	<p>Academy leadership would observe that trials of home environmental interventions are a special case of RCT because the interpretation of the result requires knowing whether the intervention group experienced significantly greater reductions in the target allergen(s) than the control group. Moreover, Academy leadership would comment that the degree of difference in allergen reduction between the control and intervention groups is also important in interpretation of the trial result. For example, for a trial that is "positive", if there is no difference in allergen reduction between the two groups, this suggests that the effects of the active intervention were not likely mediated by effects on the allergen and were more likely mediated by some other change. On the other hand, if the trial is negative," if there is no difference between the two groups in terms of allergen reduction, then this suggests that the negative trial may have been due to a lack of effect on the exposure. This feature that the intervention is intended to operate through the exposure is not the case in drug trials. Academy leadership would note that although there are certainly issues with adherence to the drug in drug trials, this by and large is a very small issue because adherence is tracked closely and participants enrolled in trials tend to have high medication adherence. Academy leadership would observe that this systematic review would benefit from including a discussion about this important feature of environmental trials and by revising the tables summarizing the trial findings to include a column about the effect of the intervention on allergen levels. Academy leadership would further comment it is expected that allergen levels must decrease by a substantial amount (at least 50% if not more) in order to be associated with a clinical effect, so the degree of reduction in the treatment group as compared to the control group would also be important to include, in addition to whether the difference were statistically significant.</p>	<p>We agree that the actual extent of allergen reduction achieved in a patient's home is an important mediating factor in evaluating these interventions. We have included substantial data about allergen reduction, when available, in the Strength of Evidence tables and in the Appendices. We note that there is no widely agreed upon threshold for a clinically meaningful reduction in allergen levels, and we have added the following text about this point in the Discussion.</p> <p>"However, there are no agreed upon standards for the outcomes that were most frequently reported as improved in the studies we reviewed, including measures of exacerbations, absenteeism, peak flow, asthma symptoms, and allergen reduction. Establishment of thresholds for identifying clinically significant change in a wide range of outcomes is needed."</p>

Source: <https://effectivehealthcare.ahrq.gov/topics/asthma-nonpharmacologic-treatment/final-report-indoor-allergen-reduction>

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Commentator & Affiliation	Section	Comment	Response
Public Reviewer 11 David Peden on behalf of AAAAI	Methods	Further, Academy leadership would question at least one of the pre-specified outcomes described under, “Studies had to report on the outcomes pre-specified in our PICOTS.” Academy leadership would comment regarding the statement, “Duplicate abstraction on a 10-percent random sample was used to ensure accuracy,” under Data Extraction. What was the inter-rater reliability? Further, why not duplicate for all data abstraction?	The selection of outcomes was designed to focus on validated and relevant asthma measures that are consistent with existing frameworks for assessing asthma outcomes, as proposed in Busse et al. (Journal of Allergy and Clinical Immunology, 2012, 129:S1-8). All data that were used to assess the strength of evidence or inform our findings were audited to ensure accuracy following abstraction. Data that were included in the appendix for general informative purposes but were not incorporated into our analyses were checked for accuracy through a 10 percent random sample audit. We did not measure inter-rater reliability because the second reviewer evaluated the accuracy of the first reviewer’s data, and did not conduct an independent abstraction of data. This is an effective approach for achieving efficiency and quality control.

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Commentator & Affiliation	Section	Comment	Response
Public Reviewer 11 David Peden on behalf of AAAAI	Methods	Academy leadership would also comment upon “Data Synthesis” and the statement, “In the Strength of Evidence tables, we noted any cases where a statistically significant result was not associated with an absolute difference of at least ten percent (between groups or above baseline, depending on the comparison), for the critical outcomes.” How was ten percent selected for the clinically important difference? Academy leadership would suggest that this should be specific to the outcome (e.g. MID for ACQ=0.5)?	Thank you for your comments. We used established thresholds for assessing clinically important differences for several important outcome measures, including a value of 0.5 for the ACQ. These thresholds are documented in a new Appendix E. However, for most of the asthma outcomes for which improvement was reported in this manuscript, thresholds are not established. Our study team methodologists selected a 10 percent threshold as a basic, standardized criterion across those endpoints for which no existing thresholds were identified. We revised the Methods to clarify our approach.
Peer Reviewer 1	Results	1. It is interesting that the authors chose to suggest that the cost of carpet removal might be an interference in patient adherence; however, there were no studies included that involved carpet removal as the sole intervention. Similarly, there were no studies using sole removal of pet and mold, so the comments should clearly and definitively state this upfront. As it is, the document makes it sound like the absence of studies equates with lack of efficacy, which is inaccurate.	We revised the report and do not discuss the cost of carpet removal as a specific barrier to adherence, although we do note that removing carpet is a structural change that may not be within the control of renters. We also added text to emphasize the lack of studies addressing many of the interventions, and revised the report to better clarify the distinction between a lack of evidence, and studies that demonstrate a lack of efficacy.
Peer Reviewer 1	Results	2. In table 2 there is a “New Zealand” in the list, which is collapsed into “Australia” in the total line. Might want to state “New Zealand/Australia” in the total group (or just list a separate “New Zealand” in the total).	We revised the table to include “Australia/New Zealand”.
Peer Reviewer 1	Results	3. In Table 10, page 41, line 46, “Reduced used of any...” should be “Reduced use of any....”	Thank you, we have corrected that error.

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Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 2	Results	Amount of detail and study characteristics are clearly articulated and summarized in multiple logically organized tables. Inclusion / Exclusion strategies were clear.	Thank you.
Peer Reviewer 3	Results	The key messages are clear but I have problems with some of them.	The key messages have been extensively revised.

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Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 4	Results	<p>There is no reference to seminal early papers on allergen avoidance and symptom control. The efficacy of allergen avoidance in mite-sensitive patients was demonstrated in the 1980's by the decrease in bronchial hyper-reactivity and other indices of airway inflammation after moving to mite free environments, such as high altitudes and hospital rooms. These early results were followed up by studies in the 1990's. These would probably be included as multicomponent studies.</p> <p>Some of the references are: Vervloet D, Penaud A, Razzouk H, et al. Altitude and house dust mites. J Allergy Clin Immunol. 1982;69:290e296 (IIb).</p> <p>Piacentini GL, Vicentini L, Mazzi P, Chilosi M, Martinati L, Boner AL. Miteantigen avoidance can reduce bronchial epithelial shedding in allergic asthmatic children. Clin Exp Allergy. 1998;28:561e567 (IIb).</p> <p>Platts-Mills TA, Tovey ER, Mitchell EB, Moszoro H, Nock P, Wilkins SR. Reduction of bronchial hyperreactivity during prolonged allergen avoidance. Lancet. 1982;2:675e678 (IIb).</p> <p>Peroni DG1, Boner AL, Vallone G, Antolini I, Warner JO. Effective allergen avoidance at high altitude reduces allergen-induced bronchial hyperresponsiveness. Am J Respir Crit Care Med. 1994 Jun;149(6): 1442-6.</p> <p>Benckhuijsen J1, van den Bos JW, van Velzen E, de Bruijn R, Aalbers R. Differences in the effect of allergen avoidance on bronchial hyperresponsiveness as measured by methacholine, adenosine 5'-monophosphate, and exercise in asthmatic children. Pediatr Pulmonol. 1996 Sep;22(3):147-53.</p>	<p>We recognize that numerous studies have examined the effect of allergen avoidance on pulmonary function and symptom control. In order to best support the development of updated NHLBI guidelines, we restricted our review to interventional studies that examined a pre-specified set of allergen reduction interventions and reported on the primary outcomes of interest as described in the Methods section. Each of the studies you identified examined interventions, such as isolation in high-altitude environments, that are outside the scope of this report.</p>

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Commentator & Affiliation	Section	Comment	Response
TEP Reviewer 1	Results	In the discussion of allergen interventions, it would be important to not only list whether a reduction in a particular allergen was significant, but also clinically relevant. For example, there have been studies to suggest certain levels of house dust mite allergen or cat allergen that can invoke symptoms. There is no mention of whether the reductions in allergens were to levels not expected to induce symptoms.	We agree that the actual extent of allergen reduction achieved in a patient's home is an important mediating factor in evaluating these interventions. We have included substantial data about allergen reduction, when available, in the Strength of Evidence tables and in the Appendices. We note that there is no widely agreed upon threshold for a clinically meaningful reduction in allergen levels, and we have added text about this point in the Discussion
TEP Reviewer 1	Results	In the allergen intervention piece, the tables list whether specific interventions resulted in outcomes that were statistically significant. However, an indication of the patients enrolled in regards to these outcomes at baseline would be helpful. For example, it is hard to show an effect on asthma exacerbations if you enroll patients that do not have a history of exacerbations. Similarly, if patients had fairly well controlled asthma, a change in AQLQ may not occur.	We agree that these are important limitations. We considered baseline levels of the primary outcomes as part of our assessment of the evidence, in accordance with the AHRQ methods of evaluating strength of evidence.

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Commentator & Affiliation	Section	Comment	Response
TEP Reviewer 2	Results	trials of home environmental interventions are a special case of RCT because the interpretation of the result requires knowing whether the intervention group experienced significantly greater reductions in the target allergen(s) than the control group. Moreover, the degree of difference in allergen reduction between the control and intervention groups is also important in interpretation of the trial result. For example, for a trial that is "positive", if there is no difference in allergen reduction between the two groups, that suggests that the effects of the active intervention were not likely mediated by effects on the allergen and were more likely mediated by some other change. On the other hand, if the trial is "negative," if there is no difference between the two groups in terms of allergen reduction, then this suggests that the negative trial may have been due to a lack of effect on the exposure. This feature - that the intervention is intended to operate through the exposure is not the case in drug trials. Although there are certainly issues with adherence to the drug in drug trials, this by and large is a very small issue because adherence is tracked closely and participants enrolled in trials tend to have high medication adherence. This systematic review would benefit from including a discussion about this important feature of environmental trials and by revising the tables summarizing the trial findings to include a column about the effect of the intervention on allergen levels, We expect that allergen levels must decrease by a substantial amount (at least 50% if not more) in order to be associated with a clinical effect, so the degree of reduction in the treatment group as compared to the control group would also be important to include - in addition to whether the difference were statistically significant.	We agree that the actual extent of allergen reduction achieved in a patient's home is an important mediating factor in evaluating these interventions. We have included substantial data about allergen reduction, when available, in the Strength of Evidence tables and in the Appendixes. We note that there is no widely agreed upon threshold for a clinically meaningful reduction in allergen levels, and we have added text about this point in the Discussion.



Commentator & Affiliation	Section	Comment	Response
TEP Reviewer 2	Results	<p>There are some recent trials that are important and should be added to the systematic review. Two were positive single allergen intervention trials. These include the following:</p> <p>-Rabito FA, Carlson JC, He H, Werthmann D, Schal C. J Allergy Clin Immunol. 2017 Jan 10. pii: S0091-6749(16)31349-5. doi: 10.1016/j.jaci.2016.10.019. [Epub ahead of print] PMID: 28108117</p> <p>-Matsui EC, Perzanowski M, Peng RD, Wise RA, Balcer-Whaley S, Newman M, Cunningham A, Divjan A, Bollinger ME, Zhai S, Chew G, Miller RL, Phipatanakul W. JAMA. 2017 Mar 14;317(10):1027-1036. doi: 10.1001/jama.2016.21048. PMID: 28264080</p> <p>-Murray CS et al https://www.ncbi.nlm.nih.gov/pubmed/28282501#</p>	<p>The searches were updated during the peer review period. Each of the studies you suggest were identified by the searches and added to the report.</p>
TEP Reviewer 2	Results	<p>There are some studies that I didn't see included as reviewed:</p> <p>-Shirai: https://www.ncbi.nlm.nih.gov/pubmed/15888829</p> <p>-Butz AM, Matsui EC, Breysse P, Curtin-Brosnan J, Eggleston P, Diette G, Williams D, Yuan J, Bernert JT, Rand C. Arch Pediatr Adolesc Med. 2011 Aug;165(8):741-8. doi: 10.1001/archpediatrics.2011.111. Erratum in: Arch Pediatr Adolesc Med. 2011 Sep;165(9):791. PMID: 21810636</p>	<p>The Shirai study was added to the report during the peer review period. The Butz study was reviewed and excluded because it focuses on tobacco smoke as an inhaled irritant, and this is outside the scope of the review.</p>
TEP Reviewer 3	Results	<p>Figure 2 - would provide 2 figures here - 1 for each of the KQs. Combining these does not provide enough detail for the respective KQs.</p>	<p>We have separated the document into two distinct reports, one for each KQ, for clarity and ease of use.</p>



Commentator & Affiliation	Section	Comment	Response
TEP Reviewer 3	Results	Pg 14 - key points - for several of these, there are listed multiple outcomes that seem to favor the intervention. What metric was used to determine if an approach/ intervention was felt to be effective overall. It is not easy to tell if any of these were "felt" to be sufficiently effective to be used in clinical care. What outcomes "matter most"? For air purification devices, for example, does reduced school absenteeism trump no effect on exacerbations?	We selected outcomes to focus on validated and relevant asthma measures that are consistent with existing frameworks for assessing asthma outcomes, as proposed in Busse et al. (Journal of Allergy and Clinical Immunology, 2012, 129:S1-8). We chose five primary outcomes for assessment: asthma control, exacerbations, healthcare utilization, quality of life, and pulmonary physiology. Our analysis did not weight any of these primary outcomes above another, although we did prioritize these ahead of the secondary outcomes of asthma symptoms and allergen reduction. Our report does not address whether and how one primary outcome might matter more than another.
TEP Reviewer 3	Results	Pg 25 - line 47 - the home visits/community workers providing education are likely very important in the efficacy of any of the interventions. Excluding them from consideration may lessen the efficacy of any of the approaches when added to clinical care without such education support. This is noted pg 46, lines 9-10.	We agree that the role of community health workers may be important, and we noted their involvement in the included studies. They were excluded from the analysis because their role has traditionally focused on patient education for self-care rather than implementation of interventions, and this was outside the scope of interventions included in our report. As you note, the effectiveness of the included interventions may be influenced by the role of home visits, and we address this as a limitation in the Discussion.
TEP Reviewer 4	Results	I liked the way the results were presented. I think it demonstrated the difficulty of combining different studies because of a lack of between study consistencies.	Thank you.

Source: <https://effectivehealthcare.ahrq.gov/topics/asthma-nonpharmacologic-treatment/final-report-indoor-allergen-reduction>

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Commentator & Affiliation	Section	Comment	Response
TEP Reviewer 5	Results	Amount of detail is appropriate. Study characteristics are well described.	Thank you.
TEP Reviewer 6	Results	Presentation is clear. Figure 2 is quite helpful. Results are listed by key question and this improves readability. I like how the multi-component interventions are addressed separately - these have the highest clinical relevance since providers rarely recommend one intervention alone.	Thank you.
Public Reviewer 6 Tonya Winders on behalf of the Allergy and Asthma Network	Results	Based on the evidence presented and anecdotal experience, we agree with the report affirming single component allergen interventions are often ineffective. Multiple component allergen environmental control is more effective when based on testing.	Thank you.

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Commentator & Affiliation	Section	Comment	Response
Public Reviewer 7 Susan Rappaport on behalf of the American Lung Association	Results	The following comments are more specifically related to the discussion on allergens: First, trying to establish or comment on the effect of a single allergen reduction during a multi-allergen intervention really should not be used in a document like this as it is purely speculative. (page 14). Since most study outcomes are considered to be “insufficient,” (Table 10), a brief discussion of examples of why studies are “insufficient” would be helpful, especially since most studies are graded that way.	We undertook four different approaches to attempt to analyze the multicomponent studies. First, we attempted to group the studies into “bundles” based on shared components, but this was not feasible because the specific combinations of interventions were too diverse. Then we compared studies that had positive findings with studies that had no effect, and attempted to identify differences between the interventions used, but this analysis did not detect any patterns associated with positive results. Since these approaches did not enable further analysis, we evaluated the studies by active component, which provided a more useful framework. We agree that this strategy limits the robustness of our evaluation, and we note this limitation in the report. During peer review we also conducted a Qualitative Comparative Analysis to augment the analysis. All of these approaches are not described more fully in the Results, and the limitations of our analysis is addressed in the Discussion. We also address the abundance of “insufficient” findings in the Discussion.



Commentator & Affiliation	Section	Comment	Response
Public Reviewer 7 Susan Rappaport on behalf of the American Lung Association	Results	Third, highlighting of the complex needs of low income and minority groups doesn't belong in this review. There is good evidence in the literature and in this review that single allergen interventions do not work. It is unclear why the authors propose further study in this area.	We identified the unique needs of these patient populations because they have high asthma morbidity and mortality, and they are most likely to live in poor housing conditions where indoor asthma allergens thrive. Although we did not find strong evidence supporting use of single interventions, our results show that the evidence for many outcomes across most interventions is insufficient, or no evidence exists at all. We therefore suggest that there are, in general, important evidence gaps that require further research, even for single interventions.
Public Reviewer 7 Susan Rappaport on behalf of the American Lung Association	Results	Lastly, there is no mention of the fact that in studies with "sham" interventions, household allergen reduction occurs even in the sham group (Morgan study and DiMango study). This important point should be mentioned in the document.	We agree that this is an important point and have added text to the Discussion section.
Public Reviewer 8 Robert Barker on behalf of AFMA	Results	AFMA shares CRI's strong interest in evidence-based solutions for reduction of asthma morbidity and, to this end, urges the full and careful consideration of relevant science-based findings. Current scientific information does not support carpet removal as an effective mitigation strategy for indoor inhalant allergens. This is substantiated by the draft report's findings that there is no conclusive evidence regarding carpet removal as an effective remediation for allergy sufferers.	Thank you.
Public Reviewer 8 Robert Barker on behalf of AFMA	Results	As delineated in the CRI SIP, research indicates that proper cleaning and maintenance of carpet can be effective in reducing exposure to indoor inhalant allergens for asthma control and other relevant outcomes. Thus, because of the high surface area of carpet fibers, carpet may even have a beneficial effect by adsorption and trapping of inhalant allergens and allowing their removal during cleaning.	Thank you

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Commentator & Affiliation	Section	Comment	Response
Public Reviewer 9 Joe Yarbrough on behalf of CRI	Results	The findings of this review highlight the fact that considerable doubt exists regarding the evidence for carpet removal as a strategy to improve asthma control or prevent exacerbations in both children and adults. For all direct measures of asthma outcomes, the Draft Report correctly found that the strength of evidence for asthma control was either “not evaluable” or “insufficient.” The evidence base as a whole is insufficient to support meaningful conclusions about the effectiveness of carpet removal as a strategy for improving patient outcomes by reducing environmental allergen exposure.	We note that no studies were identified that examined carpet removal as a solitary intervention for improving asthma outcomes. In multicomponent studies that included carpet removal, results were heterogenous and the evidence was insufficient for the clinical outcomes we reviewed, although the studies were associated with reduced levels of house dust mite allergens. Overall, more research is needed.
Public Reviewer 9 Joe Yarbrough on behalf of CRI	Results	Although we agree with the evaluations in the Draft Report of the individual studies, we urge you to downgrade the classification of the strength of evidence for the effect of carpet removal on secondary measures (allergen levels) below the level of “moderate.” As noted in the Draft Report, several of these studies did not require carpet removal as part of the intervention. We commend AHRQ for applying their evidence review methodology strongly and consistently and identifying the limitations of these studies. Because treatment was applied inconsistently, we are concerned that the current classification level of “moderate” overstates the strength of evidence. This classification may be confusing for policymakers designing guidelines and could lead to the development of misinformed policies. Consistent with the evidence, we urge you to downgrade the strength of evidence classification for carpet removal on allergen levels below the level of “moderate.”	We have reviewed our grading of this outcome and maintain that an overall assessment of Moderate evidence accurately reflects the approach we applied consistently throughout the review, based on the AHRQ methods for assessing strength of evidence..
Public Reviewer 9 Joe Yarbrough on behalf of CRI	Results	Additionally, while the limitations of these studies are clear in the body of the report, they may not be apparent to a casual reader of the tables, specifically Table 10. We request that the limitations of the studies as reported in the text of the document also be made abundantly clear in the tables that accompany the text.	We have carefully considered the optimal approach for presenting the most relevant information as succinctly as possible in the tables. Appendix C includes detailed assessments of the risk of bias for each included study.

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Commentator & Affiliation	Section	Comment	Response
Public Reviewer 11 David Peden on behalf of AAAAI	Results	<p>Academy leadership would note that there are some important recent trials that should be added to the systematic review. Two were positive single allergen intervention trials. These include the following:</p> <p>Rabito FA, Carlson JC, He H, Werthmann D, Schal C. J Allergy Clin Immunol. 2017 Jan 10. pii: S0091-6749(16)31349-5. doi: 10.1016/j.jaci.2016.10.019. [Epub ahead of print] PMID: 28108117</p> <p>Matsui EC, Perzanowski M, Peng RD, Wise RA, Balcer-Whaley S, Newman M, Cunningham A, Divjan A, Bollinger ME, Zhai S, Chew G, Miller RL, Phipatanakul W. JAMA. 2017 Mar 14;317(10):1027-1036. doi: 10.1001/jama.2016.21048. PMID: 28264080</p> <p>Murray CS et al https://www.ncbi.nlm.nih.gov/pubmed/28282501#</p> <p>Additional studies that Academy leadership would recommend be reviewed include:</p> <p>Jhun I , Gaffin JM, Coull BA, Huffaker MF, Petty CR, Sheehan WJ, Baxi SN, Lai PS, Gold DR, Koutrakis P, Kang C, Wolfson M, Phipatanakul W. School Environmental Intervention to Reduce Particulate Pollutant Exposures for Children with Asthma. J Allergy Clin Immunol in Practice 2017;5: 154-9.</p> <p>Shirai: https://www.ncbi.nlm.nih.gov/pubmed/15888829</p> <p>Butz AM, Matsui EC, Breysse P, Curtin-Brosnan J, Eggleston P, Diette G, Williams D, Yuan J, Bernert JT, Rand C. Arch Pediatr Adolesc Med. 2011 Aug;165(8):741-8. doi: 10.1001/archpediatrics.2011.111. Erratum in: Arch Pediatr Adolesc Med. 2011 Sep;165(9):791. PMID: 21810636</p>	<p>The literature searches were updated during the peer review period. We identified and included the studies by Rabito, Matsui, Murray, and Shirai. We reviewed and excluded the study by Butz because it focuses on tobacco smoke as an inhaled irritant, which is outside the scope of this review. Similarly, the study by Jhun addresses particulate pollutants, which are not within the scope of our review as described in the Methods section.</p>

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Commentator & Affiliation	Section	Comment	Response
Public Reviewer 12 Melanie Carver on behalf of AAFA	Results	Many of the studies referenced in this draft looked at individuals who were sensitized to various allergens, but the studies did not demonstrate that the subjects were actually allergic (i.e., symptomatic when exposed to the allergen). Without knowing if the subjects are truly allergic to the allergen, it is hard to determine if the allergen reduction strategies were effective or ineffective.	We acknowledge that the lack of data confirming the allergic status of patients is a significant limitation, and address this in the Discussion.
Public Reviewer 12 Melanie Carver on behalf of AAFA	Results	Another issue is that many of the studies were using early generation allergen reduction products that were not uniform from study to study and were unproven as to whether they effectively reduced allergens. We encourage further research on asthma control that uses products that have been tested in a standardized way and proven to reduce allergens.	We agree that this is an important point, and have added the following text addressing this to the Discussion. “Finally, researchers have been examining allergen reduction strategies for several decades. This long-term history presents its own challenge, because some of the studies we reviewed include earlier versions of interventions that have likely evolved since they were studied initially.”
Peer Reviewer 1	Discussion	1. The statement on page 55 (lines 43-45) that “This review raises important questions about the effectiveness...” is not really accurate. In reality, this review has demonstrated the lack of appropriate studies to even begin to really assess the effectiveness of allergen control strategies. This type of wording should be significantly toned down throughout the document (remember, that the studies did not adequately identify subjects and failed to adhere to “common allergy-control strategies” — at least in terms of what is suggested in practice parameters for the field).	We agree that there are substantial research gaps for many of the interventions and outcomes, and we highlight the need for additional research. However, for some interventions there is evidence demonstrating lack of efficacy as well.

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Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 1	Discussion	2. There is not a specific "Future Research" section; however, there is a comment in the "Evidence Gaps" section that "several evidence gaps could benefit from future research." The manuscript goes on to discuss problems with age classifications, and a general need for "across the board...further high-quality RCTs." However, this entire paragraph (page 57, lines 8-32) seems fairly simple given the significant lack of appropriate studies. This section should be significantly and markedly increased with a much stronger call for more studies. At the risk of being redundant, it would be important to call out the marked lack of appropriate studies in the allergen reduction arena again, and then go into the research needs in this area.	We have expanded this section of the Discussion to address other opportunities for research suggested by the peer and public reviewers.
Peer Reviewer 1	Discussion	3. It is important to note that sensitization does not equate to allergic disease (see my comments in the Methods section), and that this is a major shortcoming of any attempt to determine the utility of allergen reduction in the home (and would likely be a problem in a clinical setting, given that a challenge would likely be difficult to perform).	We have added the following text to the Discussion addressing this limitation of the evidence base. "Although sensitization to common indoor inhalant allergens was measured in most studies we evaluated, sensitization is a proxy measure that does not perfectly predict whether a patient will have an allergic reaction when exposed under real-world conditions, nor does sensitization precisely identify the severity of a potential reaction."
Peer Reviewer 2	Discussion	Implications and limitations were clearly considered.	Thank you.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 2	Discussion	In the Discussion on allergen reduction, I would expand a little bit on the idea that we do not really know "how low is enough". That is many of the interventions summarized reduce ambient allergen levels, but may not have translated into clinically significant benefits because a critical threshold was not reached. This is alluded to already (e.g. p.57, lines 27-33), but it might help the general reader to make this distinction more explicit.	We have expanded the Discussion section to address this important issue. ““However, there are no agreed upon standards for the outcomes that were most frequently reported as improved in the studies we reviewed, including measures of exacerbations, absenteeism, peak flow, asthma symptoms, and allergen reduction. Establishment of thresholds for identifying clinically significant change in a wide range of outcomes is needed.””
Peer Reviewer 2	Discussion	I would also reference in this section the idea that we need to consider not only allergen levels but also microbe/allergen interactions in this regard (e.g. PMID 24908147).	Thank you for your suggestion. We agree that there are numerous additional factors, including bacteria, that interact with allergens and contribute to asthma morbidity. We have added text to the Discussion addressing these factors.
Peer Reviewer 3	Discussion		



Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 3	Discussion	<p>“Key Messages</p> <ul style="list-style-type: none">• Single interventions designed to reduce indoor allergen exposure may have little effect on asthma outcomes.• Multicomponent interventions that bundle more than one strategy may improve some asthma outcomes, but it is unclear which components are most important.• The evidence base for both single and multicomponent interventions is insufficient for addressing many primary outcomes.” <p>I am confining my comments to the population health/built environment aspects. I did not review the first version.</p> <p>On the allergens exposure/ intervention issues, most of the manuscript is more or less true, however, the situation is not as simple as portrayed. I was surprised that the review team did not consider the clinical practice parameters from the AAAAI as authoritative reviews. Parameters exist for furry pets (Ann Allergy Asthma Immunol 108:223), rodents (Ann Allergy Asthma Immunol 109:375), cockroaches (J Allergy Clin Immunol 132:802) and house dust mites (Ann Allergy Asthma Immunol 111:465). On many points, the present review is contradicted by the AAAAI parameters. Since these go through ‘triple peer review’ (the Joint Task Force, public comment, journal editorial process), the principal recommendations were very carefully looked at by many. From a governance perspective, it is a concern that HHS would advance information that contradicts that of practicing allergists in the country, without comment or explanation.</p>	<p>We are grateful that you support the accuracy of the report in general. We have added text to the Discussion about the differences in the evidence and methods used for our report and the evidence and methods that informed the previous NHLBI guideline and American Academy of Allergy Asthma and Immunology clinical practice parameters. We note that our report is a comparative effectiveness review designed to summarize and synthesize existing evidence. The report is not a clinical practice guideline, and makes no recommendations regarding how clinicians should provide clinical care.</p>

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 3	Discussion	It is also important to remember that studying housing and health is not really possible in a double blinded placebo controlled fashion hence most studies are ecological in nature. Studies that undertake remediations (as for example mold and moisture), are fraught with legal, ethical and financial issues. One study I am aware of indicated that to fix according to code mold and moisture problems in a class of homes in a city in the northeast would have cost \$20k on average per house. All relevant cognizant authorities accept that mold and dampness is harmful to health (see for example WHO guidelines for indoor air quality: dampness and mould, 2009; DHHS (NIOSH) Publication No. 2013–102; Environ Health Perspect 119:748; J Allergy Clin Immunol Pract 4:396. This is based on many well-designed studies done in different populations over the last 3 decades and a reasonably clear understanding of the mechanisms (J Allergy Clin Immunol Pract 4:386tc.).	We agree that there are many substantial challenges to conducting research in this field. Nevertheless, we did identify and include in the report numerous double blinded placebo controlled studies of interventions to reduce allergen exposure and improve asthma outcomes.
Peer Reviewer 3	Discussion	Taking out carpeting is also pretty expensive (what is under the carpet that needs to be fixed) but there is no doubt that reducing settled dust lowers exposure to all manner of things e.g. house dust mites (from the AAAAI parameter) “Carpeting: For most regions, carpeting is a major risk factor for dust mites. Carpeting not only serves as a reservoir for dust, but also provides a protective microclimate to the dust mites. Hardwood floors can easily be swept, but dust mites can burrow deep into the carpet and often are protected from effective removal by traditional vacuum cleaners. Even if HEPA vacuum cleaners remove allergens, the dust mites can remain.”	Thank you for your comments.



Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 3	Discussion	On cockroaches, the AAAAI parameter notes: “Exposure to cockroach allergen in homes should be minimized to reduce the risk of cockroach sensitization (StrRec, B Evidence); Cockroach allergen exposure should be minimized to reduce the risk of asthma morbidity in already sensitized subjects. (Rec, B Evidence).”	We note that our review is not designed to assess the core premise of whether patients with asthma can benefit from reduced exposure to allergens; the purpose of our review is to evaluate the effectiveness of specific, practical interventions for reducing exposure and improving patient centered asthma outcomes.
Peer Reviewer 3	Discussion	Finally, as the manuscript notes, the best evidence comes from multifaceted interventions. The manuscript notes (roughly) that this makes it difficult to resolve which factor mattered most. That is indeed true. However, it is not that simple. It has long been known that concurrent endotoxin exposure reduces the concentration of house dust mite allergen needed to provoke symptoms. Comparable interactions exist in the context of exposure to the form of glucan found in the fungi that grow in damp buildings. Thus it is the nature of the population health effects observed that lowering one agent does not necessarily yield a proportionate health outcome.	Thank you for your comments. We agree that these are complex problems and we have added text to the Discussion section that further addresses the challenges of evaluating interventions in the context of the interaction between allergens, exposure mechanisms, and allergen reduction strategies.

Source: <https://effectivehealthcare.ahrq.gov/topics/asthma-nonpharmacologic-treatment/final-report-indoor-allergen-reduction>

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Peer Reviewer 4	Discussion	<p>There is no discussion of ethical issues involved in control groups for cleaning and allergen removal studies. Some discussion should be included that explains that ethics review boards (instituted universally in the 1990's) in light of the controversial lead studies, rarely allow for strict control groups in environmental exposure experiments. The types of studies that are allowed involve some variety of delay in the intervention control group. The positive end point is therefore the improvement in the intervention group that occurs ahead of similar improvement in the control group. When coupled with the placebo effect and the fact that the control group is informed that they are in a cleaning study, are educated as to the types of interventions that are occurring in the active group and are allowed to implement these interventions at will, it is very typical for both groups to achieve symptom reduction during the study. It is nearly impossible to have a true control group in an environmental study.</p>	<p>Thank you for raising this important consideration. We acknowledge the difficulty in conducting studies of environmental interventions.</p>

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Peer Reviewer 4	Discussion	Also I think you need to discuss that the methods used in the type of review you performed may not be adequate to evaluate multifactorial interventions. This should be stated as a potential weakness of the review.	We undertook four different approaches to attempt to analyze the multicomponent studies. First, we attempted to group the studies into “bundles” based on shared components, but this was not feasible because the specific combinations of interventions were too diverse. Then we compared studies that had positive findings with studies that had no effect, and attempted to identify differences between the interventions used, but this analysis did not detect any patterns associated with positive results. Since these approaches did not enable further analysis, we evaluated the studies by active component, which provided a more useful framework. We agree that this strategy limits the robustness of our evaluation, and we note this limitation in the report. During peer review we also conducted a Qualitative Comparative Analysis to augment the analysis. All of these approaches are not described more fully in the Results, and the limitations of our analysis is addressed in the Discussion.

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Commentator & Affiliation	Section	Comment	Response
TEP Reviewer 2	Discussion	Another unique aspect of environmental interventions is that it is that some subpopulations benefit more than others. For example, providing dust mite covers indiscriminately in a primary care setting to adults with asthma is not efficacious (Woodcock et al NEJM 2003), but doing a similar intervention among children who are sensitized to dust mite and have a history of an exacerbation is efficacious (Murray C AJRCCM 2017, In press). Aside from age, there are other features that appear to be important in determining efficacy, so that the population enrolled (age, whether they had to be sensitized to the allergen being targeted, whether they had to have a certain level of exposure in their homes, whether they had to meet a certain severity level of their asthma, and whether they have co-morbidities) matters when interpreting the results of a body of literature. Although there is some mention that age might be a factor, there is insufficient discussion of this point and it is an important consideration in the setting of a "negative" systematic review in which the inclusion criteria were broad and the literature that exists is heterogeneous in terms of population enrolled.	We agree that population factors such as sensitization, severity, and age can play an important confounding role when assessing the evidence base. We have presented the available study-level data about each of these factors in the appendix. We also have expanded the Discussion section to address these limitations in greater detail. For the studies of mattress covers, we would note that 16 out of 17 included studies confirmed that all patients were sensitized to dust mites. Ten of the 16 used skin prick tests, while the other studies used blood tests. As you note, however, many other features of the population are also important.
TEP Reviewer 3	Discussion	pg 46 - lines 36-46- there is no real final implication provided. The review suggests individual approaches do not work and should not be used. There is no statement in this paragraph about multi-component or tailored approaches.	We have revised the subsection on Implications for Clinical and Policy Decisionmaking in the Discussion to address some the issues that clinicians might consider in practice, such as the clinical complexity, disease severity, and home environment of their patients. It will be the role of the guideline committees to develop recommendations about specific interventions.

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Commentator & Affiliation	Section	Comment	Response
TEP Reviewer 4	Discussion	There is a problem with the future research (57 of 173) section in that the noise in these types of studies (all the other places people go-children to schools and grandma's house and adults to work- are not addressed in this section. Perhaps home environmental remediation is essential but not sufficient because of the noise in this system. Did any of the studies address the multiple location exposure problem? Perhaps this is essential to all future studies.	The lack of studies that evaluate environments outside the home is a major limitation, and we addressed this in the revised Discussion section.
TEP Reviewer 5	Discussion	The implications and limitations are clearly stated. The report is clinically meaningful overall and the examination of key question 1 is useful in that it suggests that single and multicomponent interventions may be helpful but data is insufficient.	Thank you.
TEP Reviewer 6	Discussion	Well written discussion, nice review of the strength of evidence. Limitations are clear and discussed in the context of the review process as well as the evidence base. I really like the discussion of the findings in relation to other reviews.	Thank you.
Public Reviewer 8 Robert Barker on behalf of the AFMA	Discussion	While carpet removal has not been found to produce the desired health and safety results, there is reason to believe that removal could actually be counterproductive. AFMA therefore joins CRI in urging the expeditious elimination of the current recommendation for carpet removal from the National Asthma Education and Prevention Program Guidelines for the Diagnosis and Management of Asthma.	Thank you for your comments. We did not identify any clinical studies that examined the benefits or harms of carpet removal as a solitary strategy, and the results of multicomponent studies that included carpet removal were heterogenous. We also note that this report is a systematic review of the evidence and does not make clinical recommendations for practice.



Commentator & Affiliation	Section	Comment	Response
Public Reviewer 9 Joe Yarbrough on behalf of CRI	Discussion	The Draft Report further highlights several important considerations for patients, clinicians, and policymakers. Since asthma can significantly impact overall health and quality of life, patients and their families may be motivated to adopt interventions that are not physically invasive, like carpet removal, to augment pharmacologic treatment. However, allergen-control interventions like carpet removal are expensive and may be difficult or impossible for sufferers to implement. Neither physicians nor policymakers want patients—especially those with severely constrained financial resources—to purchase interventions that are not helpful.	We agree that evidence about the effectiveness of interventions and cost are important for decision making by patients, clinicians, and policy makers.
Public Reviewer 11 David Peden on behalf of AAAAI	Discussion	Regarding the Discussion Section, Academy leadership would note that in studies that enroll low-income urban populations, the most commonly used primary outcome is days of symptoms, which is ascertained by questionnaire and not a daily symptom diary. Further, this type of outcome has been used for decades in studies enrolling this population and although not on the list of formally validated outcomes, has face validity given its performance in this population over many, many years. In fact, the "validated" measures of symptoms and quality of life have not been validated in this population and there are reasons to be concerned that they perform differently in low income minority populations than the populations for which they were validated. Academy leadership would observe that it seems that the studies that used these type of outcomes were downgraded in importance because of the definition of acceptable outcomes that was developed. Academy leadership would recommend that this definition should be reconsidered.	The outcomes were selected to focus on validated and relevant asthma measures that are consistent with existing frameworks for assessing asthma outcomes, as proposed in Busse et al. (Journal of Allergy and Clinical Immunology, 2012, 129:S1-8). Although symptom days are often used as a primary outcome in published studies, they do not represent a validated or standardized metric. We did, however, grade the evidence for symptoms for each intervention, using the same methods that were applied to the other outcomes, and found almost no high or moderate strength evidence demonstrating improvement in symptom days.

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Commentator & Affiliation	Section	Comment	Response
Public Reviewer 11 David Peden on behalf of AAAAI	Discussion	Academy leadership would also note another unique aspect of environmental interventions is that it is that some subpopulations benefit more than others. For example, providing dust mite covers indiscriminately in a primary care setting to adults with asthma is not efficacious (Woodcock et al NEJM 2003), but doing a similar intervention among children who are sensitized to dust mite and have a history of an exacerbation is efficacious (Murray C AJRCCM 2017, In press).	We agree that some interventions are likely to be most effective in specific subpopulations. However, we could not stratify most of our analyses by subgroups, including age or severity of disease, because of heterogeneity in how populations were defined and poor reporting of important demographic characteristics.
Public Reviewer 11 David Peden on behalf of AAAAI	Discussion	Further, Academy leadership would note, aside from age, there are other features that appear to be important in determining efficacy, so that the population enrolled (age, whether they had to be sensitized to the allergen being targeted, whether they had to have a certain level of exposure in their homes, whether they had to meet a certain severity level of their asthma, and whether they have co-morbidities) matters when interpreting the results of a body of literature. Academy leadership would observe that although there is some mention that age might be a factor, there is insufficient discussion of this point and it is an important consideration in the setting of a "negative" systematic review in which the inclusion criteria were broad and the literature that exists is heterogeneous in terms of population enrolled.	We agree that population factors such as sensitization, severity, and age can play an important confounding role when assessing the evidence base. We have presented the available study-level data about each of these factors in the appendix. We also have expanded the Discussion section to address these limitations in greater detail. For the studies of mattress covers, we would note that 16 out of 17 included studies confirmed that all patients were sensitized to dust mites. Ten of these 16 used skin prick tests, while the other studies used blood tests. As you note, however, many other features of the population are also important.



Commentator & Affiliation	Section	Comment	Response
Public Reviewer 12 Melanie Carver on behalf of AAFA	Discussion	The studies reviewed in this draft have known limitations, unknown consistency and are imprecise. AAFA discourages drawing conclusions from a collection of very limited and inconsistent studies. This draft shows there are limited data providing evidence for single intervention measures; but does not show any evidence against single intervention measures to reduce allergens. Multicomponent interventions may be more valuable, with studies showing improvement in various outcomes when using combinations of interventions such as air purification devices, HEPA vacuums, mattress covers, and pest control strategies.	Thank you for your comments.
Peer Reviewer 1	Clarity and Usability	It really isn't helpful to have these two interventions combined in a single report. As it is written it almost seems like the report is saying telling patients and physicians that allergen reduction doesn't work for asthma, but bronchial thermoplasty does. That is clearly not the intent of the AHRQ, but nonetheless that is how the report reads (and, in fact, is what the Key Messages on page 2 appear to indicate).	We have separated the document into two distinct reports for clarity and ease of use.
Peer Reviewer 1	Clarity and Usability	As mentioned previously, the problem with the report is equating lack of appropriate studies with lack of efficacy in allergen reduction. The real message in terms of the allergen reduction (KQ1) should be that much more research needs to be undertaken before any recommendations for or against allergen reduction can be made (with an explanation of the current shortcomings in the studies).	Thank you for your suggestion. We have revised the text in the Key Points, Results, and Discussion to clarify the distinction between a lack of evidence, and evidence for no effect.
Peer Reviewer 2	Clarity and Usability	Very well done in terms of clarity and usability.	Thank you.
Peer Reviewer 3	Clarity and Usability	The report is very clear.	Thank you.

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Peer Reviewer 4	Clarity and Usability	The goals of the review are well stated. However, the form is very dry and quite difficult to follow. The frequent use of acronyms requires constant referral to the glossary. I would like to see more emphasis given to the multi component studies that dominate the recent literature. Most people have quit performing the single component studies unless it is driven by a commercial product.	Thank you for your review. We have reduced the use of acronyms throughout the reports. We also conducted a Qualitative Comparative Analysis to better evaluate the multicomponent studies.
TEP Reviewer 1	Clarity and Usability	This is a well-written document providing some critical information to hopefully guide patient care. However, my conclusions would be that most of the recommendations we are currently using on allergen remediation are not effective. It will be of interest to see how these findings translate into the revised asthma guidelines.	Thank you for your review and feedback.
TEP Reviewer 3	Clarity and Usability	Well presented. Again, the inclusion of 2 unrelated treatment approaches makes this document a bit more difficult to read and digest than if the 2 KQ2 were presented separately.	We have separated the document into two distinct reports for clarity and ease of use.
TEP Reviewer 3	Clarity and Usability	Unfortunately, the findings do not provide much clinical guidance other than to "think twice" before recommended either of these approaches.	Thank you for your review.
TEP Reviewer 3	Clarity and Usability	Well done!	Thank you.
TEP Reviewer 4	Clarity and Usability	These types of data are repetitive but in presenting the results of each of the environmental allergens in the same way, it allows for comparison between allergens.	Thank you.
TEP Reviewer 5	Clarity and Usability	Report is well structured and organized but it is hard to follow the tables easily. Why not just summarize each outcome followed by findings with each study. Would have been helpful to have some data figures.	Thank you for your suggestion. We have attempted to revise and organize both reports to maximize their readability.
TEP Reviewer 5	Clarity and Usability	I do not believe the conclusions are relevant for either question. Reduction of allergens in the home may still be useful in a subset of patients. Why not state that?	By separating the document into two distinct reports, we have attempted to provide more relevant conclusions for readers of both reviews.
TEP Reviewer 6	Clarity and Usability	Well written and clear. This is a very important document that will be widely read and disseminated. It also highlights the gaps and need for future research.	Thank you.

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